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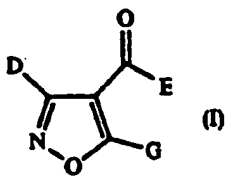
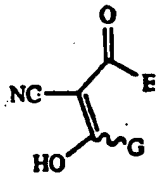
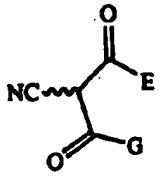


(I)



(a)



(III)

(57) Abstract

Compounds having a formula selected from the group consisting of (I), (a) and (III) and the respective pharmaceutically acceptable salts, esters and prodrugs thereof, wherein E is selected from the group consisting of $-R^{14}$, $-NR^{14}R^{15}$, $-SR^{14}$, $-OR^{14}$ and $-CR^{14}R^{15}R^{16}$ and R^{14}, R^{15} and R^{16} are independently selected from (I) hydrogen, (II) $-NR^6R^7$, (III) substitued -(C_1-to-C_{10}alkyl), (IV) substituted -(C_2-to-C_{10} alkenyl), (V) substituted -(C_3-to-C_{10} alkynyl), (VI) substituted aryl, (VII) substituted heterocyclic, (VIII) substituted biaryl, (IX) substituted -aryl-heterocyclic, (X) substituted -heterocyclic-aryl, (X) substituted -Q-aryl, (XI) substituted -Q-heterocyclic, (XII) substituted -Q-biaryl, (XIII) substituted -aryl-Q-aryl', (XIV) substituted -heterocyclic-Q-heterocyclic', (XV) substituded -heterocyclic-Q-aryl, and (XVI) substituted -aryl-Q-heterocyclic. As well as pharmaceutical composition comprising such compounds and methods for the therapeutic use thereof.

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IMMUNOSUPPRESSIVE AGENTS

This is a continuation-in-part of U.S. patent application Serial No. 08/056,500, filed May 1, 1993 and pending, which is a continuation-in-part of U.S. patent application Serial No. 08/048,499 filed on April 16, 1993 and abandoned.

Field of the Invention

The present invention relates to novel chemical compounds having immunomodulatory activity, and in particular to isoxazole and ring-opened isoxazole immunosuppressive and/or antiinflammatory agents. The invention also relates to means for the preparation of and pharmaceutical compositions containing such compounds, as well as methods of treatment employing the same.

Background of the Invention

Certain cancer chemotherapy drugs, such as methotrexate and cyclophosphamide, have been found to have immunosuppressive activity. The proposed immunosuppressive modes of action of cyclophosphamide and another cancer chemotherapeutic agent, azathioprine, have been described (Elion, G.B., Science, 244:41-47 (1989), and Clarke, L. and Waxman, D.J., Cancer Research, 49:2344-2450 (1989)). These compounds, however, may not be ideal long-term immunosuppressive agents: Methotrexate is non-selective in its antiproliferative effects and shows no more potency on lymphocytes than other cell types (Jolivet *et al.*, New Engl. J. Med., 309:1094-1104 (1983)); long-term use of methotrexate therapy, for example in rheumatoid arthritis, is therefore limited due to its toxic effects (Alarcon *et al.*, Arthritis and Rheumatism, 32:671-676 (1989)). Problems associated with cyclophosphamide include mutagenicity, carcinogenicity and the fact that its effects on lymphocytes are not rapidly reversible.

Another class of compounds having immunomodulatory activity have been identified from fermentation isolates. One such compound, cyclosporine (cyclosporin A, Borel *et al.* Immunol., 32:1017-1025 (1977)), has found widespread use since its introduction in the fields of organ transplantation and immunomodulation and has brought about a significant increase in the success rate for transplantation procedures. Cyclosporine has been found to be an inhibitor of cytokine production (reviewed by Schreiber *et al.*, Immunology Today, 13(4):136-42 (1992) and Sigal *et al.*, Ann. Rev. Immunol., 10:519-60 (1992)). However, unsatisfactory side-effects associated with cyclosporine such as nephrotoxicity (Bennett, W.M. and Pulliam, J. P. Ann. Internal Med., 99:851-854 (1983)) have led to a continued search for immunosuppressant compounds having improved efficacy and safety. This effort has resulted in the identification of a number of macrocyclic compounds isolated from the

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genus *Streptomyces*, such as the 23-membered macrocyclic lactone FK-506 and its analog FR-900520 (ascomycin), which have immunosuppressive activity. Unfortunately, these compounds, too, have demonstrated some toxicity in mammals.

Recently a class of isoxazoles has been indentified having immunosuppressant activity. These heterocycles are rapidly converted *in vivo* to ring-opened metabolites which are believed to be the active therapeutic agents. Antiinflammatory metabolites as well as the parent isoxazoles were first disclosed by Ertel *et al.* in German patent number 2555789. The first of these analogs to show promise is leflunomide (HWA-486) which has demonstrated efficacy in models of autoimmune disease, rheumatoid arthritis and allograft transplantation (Bartlett *et al.* in "Therapeutic Approaches to Inflammatory Disease", ed. Lewis, A.J. *et al.*, Elsevier, New York (1989), pp. 215-228). Leflunomide is readily converted *in vivo* to its ring-opened metabolite. Although this metabolite has a wide variety of physiological effects *in vitro*, the definitive mode of action is presently unclear. Isoxazole immunosuppressants also appear to be safer than their macrocyclic counterparts since none of the toxic effects associated with FK-506, cyclosporine or their analogs have been noted during the study of these new therapeutic agents.

Although the immunosuppressive activity of leflunomide is under study in clinical trials, its usefulness could be improved upon. The metabolite of this compound has a considerable half-life which may hamper treatment of opportunistic infections in immunosuppressed patients. Research efforts are therefore underway to discover novel isoxazoles which possess superior properties. These efforts include the preparation of ester and thioester analogs, the synthesis of prodrugs, the chemical modification of the parent isoxazole, and the synthesis of hybrid species derived from mimics of the active metabolite.

Despite these efforts, the need remains for compounds having immunosuppressive activity which do not have the serious side effects frequently associated with immunosuppressant therapy such as increased risk of malignancy or prolonged susceptibility to viral or other infections. Chronic conditions such as rheumatoid arthritis and organ transplantation where immunomodulatory drugs are taken for a number of years can lead to the already-cited complications. Optimally one would also want a drug in which the suppression of immune function was rapidly reversible. Accordingly, one object of the invention is to provide novel isoxazoles, products derived from isoxazole ring opening (and analogs thereof), and their tautomers which possess the desired immunomodulatory activity but which may be found to minimize untoward side effects.

Another object of the present invention is to provide synthetic processes for the preparation of such compounds.

A further object of the invention is to provide pharmaceutical compositions containing, as an active ingredient, one of the above compounds.

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Yet another object of the invention is to provide a method of treating a variety of disease states including resistance by a recipient patient to transplantation of organs or tissue such as heart, kidney, liver, medulla ossium, skin, cornea, lung, pancreas, intestinum tenue, limb, muscle, nervus, duodenum, small-bowel, pancreatic-islet-cell, etc.; graft-versus-host diseases brought about by medulla ossium transplantation; autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, allergic encephalomyelitis, glomerulonephritis, and the like; and further infectious diseases caused by pathogenic microorganisms. Further uses may include the treatment and prophylaxis of inflammatory and hyperproliferative skin diseases and cutaneous manifestations of immunologically-mediated illnesses, such as psoriasis, atopical dermatitis, contact dermatitis and further eczematous dermatitises, seborrheic dermatitis, Lichen planus, Pemphigus, bullous pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus, acne and Alopecia areata; various eye diseases (autoimmune and otherwise) such as keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, Scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, etc.; reversible obstructive airway disease, which includes condition such as asthma (for example, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma), particularly chronic or inveterate asthma (for example, late asthma and airway hyper-responsiveness), bronchitis and the like; inflammation of mucosa and blood vessels such as gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns and leukotriene B_4-mediated diseases; intestinal inflammations/allergies such as Coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis; food-related allergic diseases which have symptomatic manifestation remote from the gastro-intestinal tract (e.g. migraine, rhinitis and eczema); renal diseases such as interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome and diabetic nephropathy; nervous diseases such as multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis and radiculopathy; endocrine diseases such as hyperthyroidism and Basedow's disease; hematic diseases such as pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia and anerythroplasia; bone diseases such as osteoporosis; respiratory diseases such as sarcoidosis, fibroid lung and idiopathic interstitial pneumonia; skin disease such as dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris,

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photoallergic sensitivity and cutaneous T cell lymphoma; circulatory diseases such as arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa and myocardosis; collagen diseases such as scleroderma, Wegener's granuloma and Sjogren's syndrome; adiposis; eosinophilic fasciitis; periodontal disease such as lesions of gingiva, periodontium, alveolar bone and substantia ossea dentis; nephrotic syndrome such as glomerulonephritis; male pattern aleopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth; muscular dystrophy; Pyoderma and Sezary's syndrome; Addison's disease; active oxygen-mediated diseases, as for example organ injury such as ischemia-reperfusion injury of organs (such as heart, liver, kidney and digestive tract) which occurs upon preservation, transplantation or ischemic disease (for example, thrombosis and cardiac infraction): intestinal diseases such as endotoxin-shock, pseudomembranous colitis and colitis caused by drug or radiation; renal diseases such as ischemic acute renal insufficiency and chronic renal insufficiency; pulmonary diseases such as toxinosis caused by lung-oxygen or drug (for example, paracort and bleomycins), lung cancer and pulmonary emphysema; ocular diseases such as cataracta, siderosis, retinitis, pigmentosa, senile macular degeneration, vitreal scarring and corneal alkali burn; dermatitis such as erythema multiforme, linear IgA ballous dermatitis and cement dermatitis; and others such as gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution (for example, air pollution), aging, carcinogenis, metastasis of carcinoma and hypobaropathy; disease caused by histamine or leukotriene-C_4 release; Behcet's disease such as intestinal-, vasculo- or neuro-Behcet's disease, and also Behcet's which affects the oral cavity, skin, eye, vulva, articulation, epididymis, lung, kidney and so on. Furthermore, the compounds of the invention are useful for the treatment and prevention of hepatic disease such as immunogenic diseases (for example, chronic autoimmune liver diseases such as the group consisting of autoimmune hepatitis, primary biliary cirrhosis and sclerosing cholangitis), partial liver resection, acute liver necrosis (e.g. necrosis caused by toxin, viral hepatitis, shock or anoxia), B-virus hepatitis, non-A/non-B hepatitis, cirrhosis (such as alcoholic cirrhosis) and hepatic failure such as fulminant hepatic failure, late-onset hepatic failure and "acute-on-chronic" liver failure (acute liver failure on chronic liver diseases), and moreover are useful for various diseases because of their useful activity such as augmention of chemotherapeutic effect, preventing or treating activity of cytomegalovirus infection, particularly HCMV infection, anti-inflammatory activity, and so on.

Summary of the Invention

In one aspect of the present invention are disclosed compounds having the formula (I), as well as the related products of ring opening (II) and their tautomers (III),

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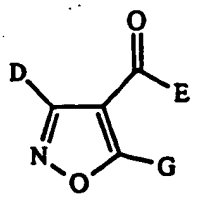
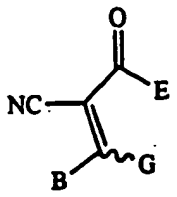
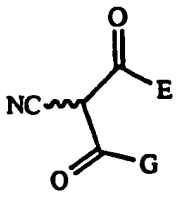


(I)
Acyl isoxazole

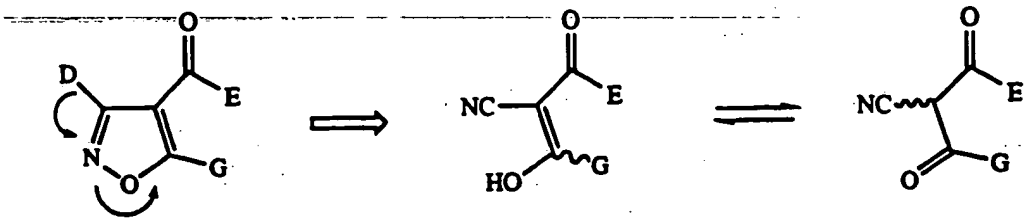


(II)
Ring-opened product



(III)
Tautomer of II

where B in formula (II) represents -OH, lower alkoxy or -O-(hydroxy-protecting group). The ring-opened products (II) where B is -OH and their tautomers (III) may arise from the parent isoxazole via the following mechanism, in the course of which functional group D is eliminated:



Alternatively, these α-cyano-β-hydroxy crotonyl analogs can be synthesized via an independent route. Also included among the compounds of the invention are the salts, esters and prodrugs of each of the above compounds.

The substituent E in the above formulae is $-R^{14}$, [redacted] $-SR^{14}$, $-OR^{14}$ or $-CR^{14}R^{15}R^{16}$, where R^{14}, R^{15} and R^{16} are independently selected from

[redacted]

(II) $-NR^6R^7$,
(III) $-(C_1\text{-to-}C_{10}\text{ alkyl})$,
(IV) $-(C_2\text{-to-}C_{10}\text{ alkenyl})$,
(V) $-(C_3\text{-to-}C_{10}\text{ alkynyl})$,

[redacted]

(VII) heterocyclic,
(VIII) biaryl,
(IX) -aryl-heterocyclic,
(X) -heterocyclic-aryl,
(X) -Q-aryl,

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(XI) -Q-heterocyclic,
(XII) -Q-biaryl,
(XIII) -aryl-Q-aryl',
(XIV) -heterocyclic-Q-heterocyclic',
(XV) -heterocyclic-Q-aryl, and
(XVI) -aryl-Q-heterocyclic.

The substituents R^6 and R^7 in the above may be hydrogen, alkyl, alkenyl, acyl, aryl, heterocyclic, biaryl, cycloalkyl, arylalkyl, hydroxyalkyl or arylsulfonyl, where each radical other than hydrogen may be substituted with between one and three substituents independently selected from the group consisting of halogen, haloalkyl, haloalkoxy, -CHO, -CN, -C(O)OH, -C(O)O-(C_1-to-C_6 alkyl), $-N_3$, $-NO_2$, -OH and oxo.

The substituent (III) in the above, -(C_1-to-C_{10} alkyl), which includes straight and branched alkyl, cycloalkyl, (cycloalkyl)alkyl, bicycloalkyl and (bicycloalkyl)alkyl, is optionally substituted with between one and six substituents independently selected at each instance from (a) R^{10}, (b) $R^{10'}$, and (c) heterocyclic, biaryl, -Q-aryl, -Q-heterocyclic, -Q-biaryl, -aryl-Q-aryl', -heterocyclic-Q-heterocyclic', -heterocyclic-Q-aryl or -aryl-Q-heterocyclic, where aryl, aryl', heterocyclic, heterocyclic' and biaryl are each independently substituted with X, Y and Z.

The substituent R^{10} in the above is selected at each instance from among (i) halogen, (ii) haloalkyl, (iii) haloalkoxy, (iv) -OH, (v) $-(CH)_mNR^6R^7$ where m is zero to six, (vi) -CHO, (vii) $-(CH_2)_mOR^6$ where m is zero to six, (viii) $-CH(OR^{12'})(OR^{12''})$ where $R^{12'}$ and $R^{12''}$ are independently -(C_1-to-C_3 alkyl) or, taken together, form an ethylene or propylene bridge, (ix) $-(CH_2)_m$-$OC(O)R^6$, (x) -CN, (xi) -C(O)OH, (xii)-C(O)O-(C_1-to-C_6 alkyl), (xiii) $-C(O)NR^6R^7$, (xiv) -(C_3-to-C_7 cycloalkyl), (xv) aryl substituted with X, Y and Z, (xvi) $-NO_2$, (xvii) $-N_3$, (xviii) guanidino optionally substituted with a substituent which may be loweralkyl, aryl, acyl, arylsulfonyl, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl or alkylsulfonyl, (xix) $-OR^{11}$, (xx) oxo, (xxi) epoxy, (xxii) thiooxo, (xxiii) -SH, (xxiv) $-S(O)_sR^6$ where s is zero, one or two, and (xxv) $-S(O)_tNR^6R^7$ where t is one or two. R^{11} in turn may be $-P(O)(OH)O^-M^+$ where M^+ is a positively charged inorganic or organic counterion, $-S(O)_2O^-M^+$ or $-CO(CH_2)_mC(O)O^-M^+$.

The substituent $R^{10'}$ in the above is selected at each instance from (i) $-(CH_2)_mNR^{6'}R^{7'}$, (ii) $-(CH_2)_mOR^{6'}$, (iii) $-(CH_2)_mOC(O)R^{6'}$, (iv) $-C(O)NR^{6'}R^{7'}$, (v) $-S(O)_tNR^{6'}R^{7'}$, (vi) $-S(O)_sR^{6'}$, (vii) aryl substituted with X', Y' and Z', and

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(viii) heterocyclic substituted with X', Y' and Z'.

The substituents X, Y, and Z in the above are each independently selected at each instance from among (a') hydrogen, (b') halogen, (c') haloalkyl, (d') -(C_1-to-C_7 alkyl), (e') -(C_2-to-C_6 alkenyl), (f')-(C_2-to-C_6 alkynyl), (g') -$(CH_2)_mNR^6R^7$, (h') -CN, (i') -CHO, (j') -$(CH_2)_mOR^6$ where m is zero to six, (k') -$(CH_2)_mC(O)OR^6$, (l') -$(CH_2)_mOC(O)R^6$, (m') -$CH(OR^{12'})(OR^{12''})$ where $R^{12'}$ and $R^{12''}$ are independently -(C_1-to-C_3 alkyl) or, taken together, form an ethylene or propylene bridge, (n') -$C(O)NR^6R^7$, (o') -NO_2, (p') -N_3, (q') guanidino optionally substituted with a substituent chosen from lower alkyl, aryl, acyl, arylsulfonyl, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl and alkylsulfonyl, (r') -OR^{11}, (s') -$S(O)_sR^6$ where s is zero, one or two, and (t') -$S(O)_tNR^6R^7$ where t is one or two. Alternatively, any two adjacent of X, Y and Z, taken together with the carbon atoms to which they are attached, may form a 5- to 7-membered ring which includes zero, one or two additional heteroatoms independently selected from among -O-, -$S(O)_s$- and -$N(R^8)$-.

The substituents X', Y' and Z' in the above are independently selected at each instance from the same groups comprised by X, Y and Z. Additionally, X', Y' and Z' may be chosen from among -$(CH_2)_mNR^{6'}R^{7'}$, -$(CH_2)_mOR^{6'}$, -$(CH_2)_mC(O)OR^{6'}$, -$(CH_2)_mOC(O)R^{6'}$, -$C(O)NR^{6'}R^{7'}$, -$S(O)_tNR^{6'}R^{7'}$ and -$S(O)_sR^{6'}$.

The divalent substituent Q in the above is independently selected at each instance from -(C_1-to-C_6 alkylene)-, -(C_2-to-C_6 alkenylene)-, -(C_2-to-C_6 alkynylene)-, -$(CH_2)_mO$- where m is zero to six, -$O(CH_2)_m$- where m is zero to six, -$N(R^8)C(O)$-, -$C(O)N(R^8)$-, -$S(O)_s$- where s is zero, one or two, -$N(R^8)$-, -$N(R^8)S(O)_t$-, -$S(O)_tN(R^8)$-, -C(O)-, -N=N- and -C(S)-.

The substituents $R^{6'}$ and $R^{7'}$ in the above are independently selected at each instance from hydrogen, aryl substituted with X, Y and Z, heterocyclic substituted with X, Y and Z, and -(C_1-to-C_{10} alkyl), where -(C_1-to-C_{10} alkyl) is optionally substituted with one to six substituents selected from among R^{10}, -$NR^8R^{8'}$, -$S(O)_sR^8$, -$S(O)_tNR^8R^{8'}$, biaryl, -Q-aryl, -Q-heterocyclic, -Q-biaryl, -aryl-Q-aryl', -heterocyclic-Q-heterocyclic', -heterocyclic-Q-aryl and -aryl-Q-heterocyclic; each such aryl, aryl', heterocyclic, heterocyclic' or biaryl radical is independently substituted with X, Y and Z.

Alternatively, $R^{6'}$ and $R^{7'}$ and the nitrogen atom to which they are attached may form a 3- to 7-membered heterocyclic ring containing zero, one or two additional heteroatoms independently selected from -O-, -$S(O)_s$- and -NR^8-. Each ring valency in the heterocyclic ring is substituted with a compatible radical which is -R^{66} or -Q-R^{66}, where R^{66} is selected

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at each instance from the group consisting of hydrogen, R^{10},-$NR^8R^{8'}$, -$S(O)_sR^8$, -$S(O)_tNR^8R^{8'}$, aryl, heterocyclic, biaryl, -aryl-Q-aryl', -h terocyclic-Q-heterocyclic', -heterocyclic-Q-aryl, -aryl-Q-heterocyclic. Again, each such aryl, aryl', heterocyclic, heterocyclic' or biaryl radical is independently substituted with X, Y and Z.

The substituents R^8 and $R^{8'}$ in the above are independently selected at each instance from hydrogen; -R^{10} other than halogen, -NO_2 or -N_3; -(C_1-to-C_6 alkyl); -(C_2-to-C_6 alkenyl) and -(C_3-to-C_6 alkynyl). Radicals -(C_1-to-C_6 alkyl), -(C_2-to-C_6 alkenyl) and -(C_3-to-C_6 alkynyl) may in turn be optionally substituted with one to three substituents R^{55} chosen from among amino, aryl, guanidino, heterocyclic, monoalkylamino, dialkylamino, acylamino, alkoxycarbonylamino, arylalkyloxycarbonylamino, aryloxycarbonylamino, acylguanidino, arylsulfonylguanidino, alkoxycarbonylguanidino, arylalkyloxycarbonylguanidino, aryloxycarbonylguanidino, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, N-alkyl-carboxamido, N,N-dialkylcarboxamido, N-arylcarboxamido and N,N-diarylcarboxamido.

Alternatively, R^8 and $R^{8'}$ and the nitrogen atom to which they are attached may form an optionally substituted 3- to 7-membered heterocyclic ring which includes zero, one or two additional heteroatoms independently chosen from -O-, -$S(O)_s$- where s is zero, one or two, and -NR^8-.

The above substituents (IV) and (V), -(C_2-to-C_{10} alkenyl) (which includes branched, unbranched, cyclic and bicyclic alkenyl) and -(C_3-to-C_{10} alkynyl) (which includes branched and cyclic alkynyl), are each optionally substituted with one to six substituents independently selected at each instance from R^{10}, $R^{10'}$, heterocyclic, biaryl, -Q-aryl, -Q-heterocyclic, -Q-biaryl, -aryl-Q-aryl', -heterocyclic-Q-heterocyclic', -heterocyclic-Q-aryl and -aryl-Q-heterocyclic. Each such aryl, aryl', heterocyclic, heterocyclic' or biaryl radical is independently substituted with X, Y and Z.

Similarly, in the above substituents (VI) through (XVI) which comprise aryl, heterocyclic, biaryl, -aryl-heterocyclic, -heterocyclic-aryl, -Q-aryl, -Q-heterocyclic, -Q-biaryl, -aryl-Q-aryl', -heterocyclic-Q-heterocyclic', -heterocyclic-Q-aryl and-aryl-Q-heterocyclic, each such aryl, aryl', heterocyclic, heterocyclic' or biaryl radical is independently substituted with X', Y' and Z'.

The substituent D in the above formulae is selected from hydrogen, loweralkyl, phenyl, 2-chlorophenyl, 2,4-dichlorophenyl, 2-chloro-4-fluorophenyl and -$C(O)R^9$, where

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R^9 is (a) hydrogen, (b) -OH, (c) $-O^-M^+$, (d) -(C_1-to-C_4 alkyl) where alkyl includes branching alkyl, (e) -(C_1-to-C_4 alkoxy) where alkoxy includes branching alkoxy, (f) -(C_1-to-C_4 hydroxyalkyl), (g) -(C_1-to-C_4 thioalkyl), (h) $-(CH_2)_{nn}$-(phenyl) where nn is zero to four, (i) $-(CH_2)_n-NR^4R^5$, (j) $-(CH_2)_m$-(morpholino), (k) $-NR^4R^5$, (l) $-C(O)NR^4R^5$, (m) $-C(O)OR^4$, (n) phenyl substituted with X, Y and Z, (o) -O-phenyl where phenyl is substituted with X, Y and Z, (p) $-O-(CH_2)_m$-(morpholino) or (q) $-S-(CH_2)_{nn}$-(phenyl). In the above, R^4 and R^5 are independently selected from among -hydrogen, -(C_1-C_6 alkyl) optionally substituted with halogen, and phenyl substituted with X, Y and Z.

The substituent G in the above formulae is chosen from among $-R^{14}$, $-OR^{14}$, $-S(O)_sR^{14}$, $-CR^{14}R^{15}R^{16}$, $-C{=}CR^{14}R^{15}$, $-C{\equiv}CR^{14}$, $-C{=}NR^{14}$, $-NR^{14}R^{15}$ and Z (a radical selected from the same groups comprised by X, Y and Z), or G may be selected from aryl, heterocyclic, biaryl, -heterocyclic-aryl, -aryl-heterocyclic, -Q-aryl, -Q-heterocyclic, -Q-biaryl, -aryl-Q-aryl', -heterocyclic-Q-heterocyclic', -heterocyclic-Q-aryl and -aryl-Q-heterocyclic, where each such aryl, aryl', heterocyclic, heterocyclic' or biaryl radical is independently substituted with X', Y' and Z'. Alternatively, G may be $-NR^{24}R^{25}$, where R^{24} and R^{25} and the nitrogen atom to which they are attached form a 3- to 7-membered heterocyclic ring including zero, one or two additional heteroatoms independently selected from -O-, $-S(O)_s$- and $-NR^8$-. In such a heterocyclic ring, each ring valency is substituted with a compatible radical independently selected at each instance from $-R^{66}$, $-Q-R^{66}$, $-R^{67}$ and $-Q-R^{67}$, where R^{67} at each instance is independently (i) $-CH(OR^{12'})(OR^{12''})$ or (ii) guanidino optionally substituted with loweralkyl, aryl, acyl, arylsulfonyl, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl or alkylsulfonyl.

The compounds encompassed by the above formulae are subject to the following provisos:

When E is $-NHCH_2$-(heterocyclic), the substituent G must be other than pyrrolyl.

When E is $-N(R^2)$-[(C_1-to-C_{10} alkylene)-C(O)O-(C_1-to-C_4 alkyl)], $-N(R^2)$-(aryl),$-N(R^2)$-(heterocyclic), $-N(R^2)$-(heterocyclic)-(aryl), $-N(R^2)$-(biaryl), $-N(R^2)$-(phenyl)-O-(aryl), $-N(R^2)$-(phenyl)-C(O)-(aryl), $-N(R^2)-C(CH_3)_2-CH_2$-(aryl), -OH, $-NH_2$, -SH, methyl, hydrogen, N-morpholino, N-thiomorpholino, or N-piperidinyl optionally substituted with -(C_1-to-C_2 alkyl), the substituent G must be other than R^{77} where R^{77} is (i) -(C_1-to-C_6 alkyl) optionally substituted with halogen, (ii) phenyl, (iii) benzyl or (iv) -(C_3-to-C_6 cycloalkyl). In the above, the substituent R^2 is chosen from among hydrogen, -(C_1-to-C_4 alkyl), phenyl, and benzyl.

When E is -S-phenyl or -O-phenyl where phenyl is substituted with X, Y and Z, the substituent G must be other than -(C_1-to-C_4 alkyl).

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When E is phenyl substituted with X, Y and Z, the substituent G must be other than -(C_1-to-C_6 alkyl) optionally substituted with halogen, -(C_1-to-C_6 alkenyl) optionally substituted with halogen, -(C_5-to-C_6 cycloalkenyl), -(C_3-to-C_6 cycloalkyl), -(phenyl)-R^{76}, -(benzyl)-R^{76} or -C(O)OR^{77}. In the above, R^{76} is selected from -C(O)R^{77}, -CN, -NO_2, halogen and -$NR^{78}R^{79}$, where R^{78} and R^{79} are -(C_1-to-C_6 alkyl) radicals which may be the same or different.

It is intended that when, in the above formulae, a symbol representing a variable radical such as Q, X, Y, Z, X', Y', Z' or R^x (where x is any integer) appears more than once in a single molecular formula, the radicals so represented may be the same or different at each instance. Also, where a bond to a chiral carbon atom in the above formulae is represented by a wavy line, both orientations are intended.

Representative of the compounds of the present invention are those selected from the group consisting of

5-Methyl-isoxazole-4-carboxylic acid 2-(4-trifluoromethylphenyl)ethylamide;
5-Methyl-isoxazole-4-carboxylic acid 2-(4-fluorophenyl)ethylamide;
5-Methyl-isoxazole-4-carboxylic acid 2-phenylpropylamide;
5-Methyl-isoxazole-4-carboxylic acid 2-(4-nitrophenyl)ethylamide;
5-Methyl-isoxazole-4-hydroxamic acid benzylamide;
5-Methyl-isoxazole-4-carboxylic acid 4-fluorophenylhydrazide;
5-Methyl-isoxazole-4-carboxylic acid (7-trifluoromethyl-1,2,3,4-tetrahydroquinolinyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (6-methyl-1,2,3,4-tetrahydroquinolinyl)amide;
5-Methyl-isoxazole-4-carboxylic acid isobutylamide;
5-Methyl-isoxazole-4-carboxylic acid (n-pentyl)amide;
5-Methyl-isoxazole-4-carboxylic acid pyrrolidinehydrazide;
5-Methyl-isoxazole-4-carboxylic acid morpholinohydrazide;
5-Methyl-isoxazole-4-carboxylic acid 4-trifluoromethylbenzimide;
5-Methyl-isoxazole-4-carboxylic acid 2-fluoroethylamide;
5-Methyl-isoxazole-4-carboxylic acid *trans*-4-(tert-butylcyclohexyl)amide;
5-Methyl-isoxazole-4-carboxylic acid *cis*-4-(tert-butylcyclohexyl)amide;
5-Methyl-isoxazole-4-carboxylic acid diethylamide;
5-Methyl-isoxazole-4-carboxylic acid ethylamide;
5-Methyl-isoxazole-4-carboxylic acid 2,2,2-trifluoroethylamide;
5-Methyl-isoxazole-4-carboxylic acid allylamide;
5-Methyl-isoxazole-4-carboxylic acid propargylamide;

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5-Methyl-isoxazole-4-carboxylic acid (acetonitrile)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-methoxyethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (3-methoxypropyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-diethoxyacetal)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-thioethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-hydroxyethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-hydroxybutyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-piperidinoethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-methylpiperazino)amide;
5-Methyl-isoxazole-4-carboxylic acid (ethylglycinate)amide;
5-Methyl-isoxazole-4-carboxylic acid (3-propionic acid)amide;
5-Methylisoxazole-4-carboxylic acid (1-piperidino)amide;
5-Methylisoxazole-4-carboxylic acid (4-chlorophenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-methylcyclohexyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-norbornyl)amide;
5-Methyl-4-{4-(3-trifluoromethylphenyl)piperazine-1-ylcarbonyl}-isoxazole;
5-Methyl-isoxazole-4-carboxylic acid (cyclobutylmethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (norephedrine)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-methoxycarbonyl-cyclohexylmethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-hydroxyphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-{(4-phenyl)-benzyl}amide;
5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-(4-phenoxy)-benzylamide;
5-Methyl-isoxazole-4-carboxylic acid {2-[(2-chloro-4-t-butyl-phenoxy)methyl]benzyl}amide;
5-Methyl-isoxazole-4-carboxylic acid (furfuryl)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-trifluoromethoxy-phenyl)hydrazide ;
5-Methyl-isoxazole-4-carboxylic acid {(-)-*cis*-myrtanyl}amide;
5-Methyl-isoxazole-4-carboxylic acid (3-aminopropyl)amide;
5-Methylisoxazole-4-carboxylic acid (4-methoxyphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid {(4S)-benzyloxazolidinone}imide;
5-Methyl-isoxazole-4-carboxylic acid (4-methylphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid {(+)-norephedrine}amide;
5-Methyl-isoxazole-4-carboxylic acid (4-ethylphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid {2-hydroxy-5-(7-chloro-6-(ethoxycarbonylmethoxy)benzisoxazol-3-yl)benzyl}amide;
5-Methyl-isoxazole-4-carboxylic acid {4-(2,3-dichloro-4-(ethoxycarbonylmethoxy)benzoyl)benzyl}amide;
5-Methyl-isoxazole-4-carboxylic acid (aziridinyl)amide;

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5-Methyl-isoxazole-4-carboxylic acid (4-hydroxyphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-phenylethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid cinnamimide;
5-Methyl-isoxazole-4-carboxylic acid 4-chlorocinnamimide;
5-Methyl-isoxazole-4-carboxylic acid {L-(S)-amphetamine}amide;
5-(3-Butenyl) isoxazole-4-carboxylic acid (4-trifluoromethylphenyl)amide;
5-Methyl-isoxazole-4-carboxylic acid cycloleucinolamide;
5-Methyl-isoxazole-4-carboxylic acid (tyrosine methyl ester)amide;
5-Methyl-isoxazole-4-carboxylic acid 1-aminohomopiperidinehydrazide;
5-Methyl-isoxazole-4-carboxylic acid (2-amino-2-norbornanecarboxylic acid)amide;
5-Methyl-isoxazole-4-carboxylic acid 2-thienylmethylamide;
5-Methyl-isoxazole-4-carboxylic acid (2,6-dimethylmorpholin-4-yl)amide;
5-Methyl-isoxazole-4-carboxylic acid 2-(N,N-dimethyl)aminoethylamide;
5-Methyl-isoxazole-4-carboxylic acid 2-cyclohex-1-enylethylamide;
5-Methyl-isoxazole-4-carboxylic acid 3-methoxypropylamide;
Ethyl 4-[3,5-di(5-methyl-isoxazole-4-carbonylamino)]-1H-1,2,4-triazolin-1-yl)benzoate]amide;
5-Methyl-isoxazole-4-carboxylic acid N-benzyl-N-norbornylamide;
5-Methyl-isoxazole-4-carboxylic acid (convolvinyl)amide;
5-Methyl-isoxazole-4-carboxylic acid 4-propylpiperidineamide;
5-Methyl-isoxazole-4-carboxylic acid {4-[(4-hydroxy-3-tert-butyl)-phenoxyethoxy]phenyl}amide;
5-Methyl-isoxazole-4-carboxylic acid 4-[2-(phenylaminocarbonyl)-propionyl]anilide;
5-Trifluoromethyl-isoxazole-4-carboxylic acid 3-methyl-1-butylamide;
5-Methyl-isoxazole-4-carboxylic acid 5-(N-morpholino)pentylamide;
5-Methyl-isoxazole-4-carboxylic acid (5-diisopropylamino-1,3,4-thiadiazol-2-yl)amide;
5-Methyl-isoxazole-4-carboxylic acid (L-proline *t* -butyl ester)amide;
5-Methyl-isoxazole-4-carboxylic acid (L-leucine-*t* -butyl ester)amide;
5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-(1-cyano)cyclopentylamide;
5-Methyl-isoxazole-4-carboxylic acid N-ethyl-N-(1-carboxyl)cycloheptylamide;
5-Methyl-isoxazole-4-carboxylic acid 4-[2-(2-methoxyethoxy)ethoxy]anilide;
5-Methyl-isoxazole-4-carboxylic acid (glycine trityl ester)amide;
5-Methyl-isoxazole-4-carboxylic acid (ketamine hydrochloride)amide;
5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-(5,6-dehydro-exo-2-norbornyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (β-alanine *t* -butyl ester)amide;
4-Trifluoromethyl benzoyl 5-methyltrifluoro-isoxazole-4-carboxamide;
3-(3-Methoxy)phenoxycarbonyl-5-methyl-isoxazole-4-carboxylic acid 3-methylbutylamide;

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3-(N,N-Dimethylaminocarbonyl)-5-methyl-isoxazole-4-carboxylic acid 3-(4-methoxyphenyl)propylamide;
3-(2-Chloro-4-fluorophenacyl)-5-methyl-isoxazole-4-carboxylic acid cyclohexylamide;
N (5-Phenyl-4-isoxazoyl)-N'-(4-toluenesulfonyl) 1,4-phenylenediamide;
5-Phenyl-isoxazole-4-carboxylic acid butylamide;
5-Trifluoromethyl-isoxazole-4-carboxylic acid (3-methylbutyl)amide;
5-(2-Methoxyphenyl)-isoxazole-4-carboxylic acid 4-(3-nitrophenyl)thiazol-2-ylamide;
2-(4-Trifluoromethylphenyl)ethyl 5-methyl isoxazole-4-carboxylate;
2-(4-Nitrophenyl)ethyl 5-methyl-isoxazole-4-carboxylate;
2-(4-Fluorophenyl)ethyl 5-methyl-isoxazole-4-carboxylate;
4-Chlorophenethyl 5-methylisoxazole-4-carboxylate;
4-Trifluoromethylphenyl 5-methylisoxazole-4-carboxylate;
Cinnamyl 5-methylisoxazole-4-carboxylate;
2-(3-Trifluoromethylphenyl)ethyl 5-methylisoxazole-4-carboxylate;
3-Phenylbutyl 5-methylisoxazole-4-carboxylate;
(3-Furanyl)methyl 5-methyl-isoxazole-4-carboxylate;
2-(1-Piperidyl)ethyl 5-methyl-isoxazole-4-carboxylate;
3-Pyridyl 5-methyl-isoxazole-4-carboxylate;
4-[2-Methyl-5-(4-nitrophenyl)oxazolyl]methyl 5-methyl-isoxazole-4-carboxylate;
7-Chloro-4-quinolyl 5-methyl-isoxazole-4-carboxylate;
2-Methoxyethyl 5-(4-nitrophenyl)isoxazole-4-carboxylate;
2-(4-Nitrophenyl)ethyl 5-trifluoromethylisoxazole-4-carboxylate;
3-Hydroxypropyl (5-phenyl-4-isoxazolyl) ketone;
2-Methylypropyl (5-trifluoromethyl-4-isoxazolyl) ketone;
1,1,2,2,3,3,3-Heptafluoropropyl (5-trifluoromethyl-4-isoxazolyl) ketone;
3-Furanyl (5-trifluoromethyl-4-isoxazolyl) ketone;
N[2-(4-Trifluoromethylphenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-(2-Phenylpropyl)-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Fluorophenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Nitrophenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-methoxycrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-ethoxycrotonamide;
N-[2-(4-Fluorophenyl)ethyl]-2-cyano-3-hydroxycrotonate;
N-[2-(4-Trifluoromethylphenyl)ethyl-2-cyano-3-hydroxycrotonate;
N-[n-Pentyl]-2-cyano-3-hydroxycrotonamide;
N-(Isobutyl)-2-cyano-3-hydroxycrotonamide;
N-(*trans*-4-tert-butylcyclohexyl)-2-cyano-3-hydroxycrotonamide;

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N-(*cis*-4-tert-butyl cyclohexyl)-2-cyano-3-hydroxycrotonamide;
N-(2-Fluoroethyl)-2-cyano-3-hydroxycrotonamide;
N,N-Diethyl-2-cyano-3-hydroxycrotonamide;
N-Ethyl-2-cyano-3-hydroxycrotonamide;
N-(2,2,2-Trifluoroethyl)-2-cyano-3-hydroxycrotonamide;
N-[2(4-Nitrophenyl)ethyl]-2-cyano-3-hydroxycrotonate;
N-Benzyl-2-cyano-3-hydroxycrotonamide;
N-Allyl-2-cyano-3-hydroxycrotonamide;
N-(2-Methoxyethyl)-2-cyano-3-hydroxycrotonamide;
N-(3-Methoxypropyl)-2-cyano-3-hydroxycrotonamide;
N-Acetonitrile-2-cyano-3-hydroxycrotonamide;
N-Propargyl-2-cyano-3-hydroxycrotonamide;
N-(2-Hydroxyethyl)-2-cyano-3-hydroxycrotonamide;
N-(4-Hydroxybutyl)-2-cyano-3-hydroxycrotonamide;
4-Trifluoromethylphenyl-2-cyano-3-hydroxycrotonimide;
3-Phenyl-1-butyl-2-cyano-3-hydroxycrotonate;
N-(Acetic acid)-2-cyano-3-hydroxycrotonamide;
N-(2-Norbornyl)-2-cyano-3-hydroxycrotoamide;
N-(3-Propionic acid)-2-cyano-3-hydroxy-crotonamide;
N-[2-(4-Chlorophenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-(2-Piperidin-1-ylethyl)-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Chlorophenyl)ethyl]-2-cyano-3-hydroxycrotonate;
N-Cyclobutylmethyl-2-cyano-3-hydroxy crotonamide;
N-(Ethylglycinate)-2-cyano-3-hydroxycrotonamide;
Cinnamyl 2-cyano-3-hydroxycrotonate;
N-(Epi-4-Carboxycyclohexylmethyl)-2-Cyano-3-hydroxycrotonamide;
N-(2-Methylcyclohexyl)-2-cyano-3-hydroxy crotonamide;
N-(2-Hydroxy-2-phenylethyl)-2-cyano-3-hydroxycrotonamide;
N-[2-(3-Trifluoromethylphenyl)ethyl]-2-cyano-3-hydroxycrotonate;
N-(Furfuryl)-2-cyano-3-hydroxy-crotonamide;
N-[2-(4-Methoxyphenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Methylphenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-((-)-cis-Myrtanyl)-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Ethylphenyl)ethy]-2-cyano-3-hydroxycrotonamide;
2-Cyano-3-hydroxy-crotonic acid aziridinyl amide;
N-[2-(4-Hydroxyphenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
2-Phenylethyl-2-cyano-3-hydroxycrotonamide;

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2-Cyano-3-hydroxycrotonic 4-chlorocinnamimide;
2-Cyano-3-hydroxycrotonic cinnamimide;
(4(S)-Benzyl-2-oxazolidinone)-2-cyano-3-hydroxycrotonimide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2',4'-dichlorophenyl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-phenylcrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4'-methoxyphenyl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4'-t-butylphenyl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(*trans*-phenylcyclopropyl)-acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-biphenyl-acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(3',4',5'-tri-methoxy-phenyl)-acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-phenylcrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4-trifluoromethylphenyl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(furan-2-yl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-5-phenyl-penta-2,4-dienoic acid amide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-methyl-penta-2,4-dienoic acid amide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-carboxyethylcrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-ethyl-oct-2-enoic acid amide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2-thienylmethyl)crotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-2,6-heptadieneamide;
(3-Furanyl)methyl 2-cyano-3-hydroxycrotonate;
2-(1-Piperidyl)ethyl 2-cyano-3-hydroxycrotonate;
3-Pyridyl 2-cyano-3-hydroxycrotonate;
4-(2-methyl-5-(p-nitrophenyl)oxazolyl)methyl 2-cyano-3-hydroxycrotonate;
7-Chloro-4-quinolyl 2-cyano-3-hydroxycrotonate;
2-(4-Nitrophenyl)ethyl 2-cyano-3-hydroxycrotonate;
2-(4-Nitrophenyl)ethyl 4,4,4-trifluoro-2-cyano-3-hydroxycrotonate;
N-Benzyl-2-cyano-3-hydroxycrotonyl hydroxamide;
N-Benzyl-2-cyano-3-hydroxycrotonyl hydroxamide;
N-(7-Trifluoromethyl-1,2,3,4-tetrahydroquinolinyl)-2-cyano-3-hydroxycrotonamide;
N-Cycloleucyl-2-cyano-3-hydroxycrotonamide;
N-(L-Tyrosinyl methyl ester)-2-cyano-3-hydroxycrotonamide;
N-(1-Homopiperidinyl)-2-cyano-3-hydroxycrotonylhydrazide;
N-[2-(2-Carboxy)norbornyl]-2-cyano-3-hydroxycrotonamide;
N-(2-Thienylmethyl)-2-cyano-3-hydroxycrotonamide;
N-(2,6-Dimethylmorpholinyl)-2-cyano-3-hydroxycrotonamide;
N-N-Dimethylaminoethyl-2-cyano-3-hydroxycrotonamide;

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N-[2-(1-Cyclohexenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-Benzyl-N-(2-norbornyl)-2-cyano-3-hydroxycrotonamide;
N-Convolvinyl-2-cyano-3-hydroxycrotonamide;
N-(4-Propylpiperidinyl)-2-cyano-3-hydroxycrotonamide;
N-{4-[(4-Hydroxy-3-*t*-butyl)-phenoxyethoxy]phenyl}-2-cyano-3-hydroxycrotonamide;
N-4-[2-(Phenylaminocarbonyl)propionyl]phenyl-2-cyano-3-hydroxycrotonamide;
N-(2-Methyl-1-amyl)-2-cyano-3-hydroxy-4,4,4-trifluorocrotonamide;
N-(5-Morpholinylamyl)-2-cyano-3-hydroxycrotonamide;
N-(5-Diisopropylamino-1,3,4-thiadiazole-2-yl)-2-cyano-3-hydroxycrotonamide;
N-(L-Prolyl *t*-butyl ester)-2-cyano-3-hydroxycrotonamide;
N-(L-Leucyl-*t*-butyl ester)-2-cyano-3-hydroxycrotonamide;
N-(1-Cyanocyclopentylmethyl)-2-cyano-3-hydroxycrotonamide;
N-[2-(1-Carboxycycloheptyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-{4-[2-(2-Methoxyethoxy)ethoxy]phenyl}-2-cyano-3-hydroxycrotonamide;
N-(Glycine trityl ester)-2-cyano-3-hydroxycrotonamide;
N-{[2-(2-Chlorophenyl)]-1-oxocyclohexan-2-yl hydrochloride}-2-cyano-3-hydroxycrotonamide;
N-(5-*exo*-Norbornen-2-yl)-N-methyl-2-cyano-3-hydroxycrotonamide;
N-(β-Alanyl *t*-butyl ester)-2-cyano-3-hydroxycrotonamide;
N-Pyrrolidinyl-2-cyano-3-hydroxy-4,4,4-triluforocrotonic acid hydrazide;
N-Morpholinyl-2-cyano-3-hydroxy-4,4,4-trifluorocrotonic acid hydrazide;
N-(3-Methylbutyl)-4,4,4-trifluoro-2-cyano-3-hydroxycrotonamide;
1-(3-Phenyl-2-cyano-3-hydroxyacryloylamido)-4-(4-toluenesulfonylamino)benzene;
N-Butyl-3-phenyl-2-cyano-3-hydroxyacrylamide;
3-Hydroxypropyl 1-(3-phenyl-2-cyano-3-hydroxyacryloyl) ketone;
2-Methylypropyl 1-(4,4,4-trifluoro-2-cyano-3-hydroxycrotonyl) ketone;
2-Methoxyethyl 3-(4-nitrophenyl)-2-cyano-3-hydroxyacrylate;
1,1,2,2,3,3,3-Heptafluoropropyl 1-(4,4,4-trifluoro-2-cyano-3-hydroxycrotonyl) ketone;
3-Furanylmethyl 1-(4,4,4-trifluoro-2-cyano-3-hydroxycrotonyl) ketone;
N-4-(3-Nitrophenyl)thiazol-2-yl 3-(2-methoxyphenyl)-3-hydroxy-2-cyanoacrylamide;
N-(4-Trifluoromethylphenyl)-5-(2-methoxyethyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2-fluorophenyl)isoxazole-4-carboxamide;
N-(4-Fluorophenyl)-5-(4-fluorophenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(carbomethoxymethyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2-carbomethoxyethyl)isoxazole-4-carboxamide;
N-(2-Pyridyl)-5-(2-benzylphenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(3-carboethoxypropyl)isoxazole-4-carboxamide;

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N-(4-*t*-Butylphenyl)-5-(methoxymethyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2-furanyl)isoxazole-4-carboxamide;
N-(2-Bromophenyl)-5-(4-hexadecyloxyphenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2,4-bis(1,1,2-trifluoro-2-chloroethoxy)phenyl) isoxazole-4-carboxamide;
N-(2-Bromophenyl)-5-(5,6,7,8-tetrahydro-2-naphthyl)isoxazole-4-carboxamide;
N-(2,5-Dimethoxyphenyl)-5-(2-thienyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(3-N,N dimethylsulfonamidophenyl)isoxazole-4-carboxamide;
N-(4-Fluorophenyl)-5-(*E* -2-phenylethylenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2-methylsulfonylphenyl)isoxazole-4-carboxamide;
N-Morpholino-5-(4-phenoxyphenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-((2-phenoxyethoxy)phenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(4-*t*-butylphenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(3-nitro-4-(2-(4-(2-(2,4,4,trimethylpentyl) phenoxy) ethoxy)phenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2-carbomethoxyphenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2-methoxyethyl)isoxazole-4-carboxamide;
N-(2-(5-(4-t-Butylphenyl)thienyl))-5-(3-butenyl)isoxazole-4-carboxamide;
N-(4-(4-Trifluoromethylphenyl)phenyl)-5-(4-cyanophenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(6-undecyl)isoxazole-4-carboxamide
N-(4-Trifluoromethylphenyl)-5-(3,5-bis(trifluoromethyl)phenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(1-adamantyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(*E* -3-pentenyl)isoxazole-4-carboxamide;
4-Trifluoromethylphenyl 5-((phenylsulfonyl)methyl)isoxazole-4-carboxylate;
α–Naphthyl 5-((thiophenyl)methyl)isoxazole-4-carboxylate;
2-Methylypropyl (5-(2-pyridyl)-4-isoxazolyl) ketone;
3-Furanyl (5-(2-propenyl)-4-isoxazolyl) ketone;
1,1,2,2,3,3,3-Heptafluoropropyl (5-cyclohexyl-4-isoxazolyl) ketone;
N-[2-(4-Trifluoromethylphenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2-fluorophenyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4-fluorophenyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-carbomethoxy crotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-5-carbomethoxy-2-pentenamide;
N-(2-Pyridyl)-2-cyano-3-hydroxy-3-(2-benzylphenyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-6-carboethoxy-2-hexenamide;
N-(4-*t*-Butylphenyl)-2-cyano-3-hydroxy-4-methoxy crotonamide;

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N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4-hexadecyloxyphenyl) acrylamid ;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2,4-bis(1,1,2-trifluoro-2-chloroethoxy)phenyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(5,6,7,8-tetrahydro-2-naphthyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2-thienyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(3-N,N dimethylsulfonamido phenyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2-methylsulfonylphenyl) acrylamide;
N-Morpholino-2-cyano-3-hydroxy-3-(4-phenoxyphenyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-((2-phenoxyethoxy)phenyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(3-nitro-4-(2-(4-(2-(2,4,4,Trimethylpentyl) phenoxy) ethoxy)phenyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2-carbomethoxyphenyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-5-methoxy-2-pentenamide;
N-(2-(5-(4-t-Butylphenyl)thienyl))-2-cyano-3-hydroxy-2,6-heptadienamide;
N-(4-(4-Trifluoromethylphenyl)phenyl)-2-cyano-3-hydroxy-3-(4-cyanophenyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-(*n*-pentyl)non-2-enamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(3,5-bis(trifluoromethyl) phenyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(1-adamantyl) acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-2,6-octadienamide;
4-Trifluoromethylphenyl-2-cyano-3-hydroxy-4-phenylsulfonyl crotonate;
α-Naphthyl 2-cyano-3-hydroxy-4-thiophenyl crotonate;
2-(4-Trifluoromethylphenyl)ethyl 2-cyano-3-hydroxy-5-methoxy-2-pentenoate;
3-Furanyl (1-cyano-2-hydroxy-2,4 pentadienyl) ketone;
2-Methylypropyl (1-cyano-2-hydroxy-2-(2-pyridyl)ethylenyl) ketone; and
1,1,2,2,3,3,3-Heptafluoropropyl (1-cyano-2-hydroxy-2-cyclohexylethylenyl) ketone;

and the respective pharmaceutically acceptable salts, esters and prodrugs thereof.

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Of these, preferred examples include those selected from the group consisting f

5-Methyl-isoxazole-4-carboxylic acid 2-(4-trifluoromethylphenyl)ethylamide;
5-Methyl-isoxazole-4-carboxylic acid 2-(4-fluorophenyl)ethylamide;
5-Methyl-isoxazole-4-carboxylic acid 2-phenylpropylamide;
5-Methyl-isoxazole-4-carboxylic acid 2-(4-nitrophenyl)ethylamide;
5-Methyl-isoxazole-4-hydroxamic acid benzylamide;
5-Methyl-isoxazole-4-carboxylic acid 4-fluorophenylhydrazide;
5-Methyl-isoxazole-4-carboxylic acid (7-trifluoromethyl-1,2,3,4-tetrahydroquinolinyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (6-methyl-1,2,3,4-tetrahydroquinolinyl)amide;
5-Methyl-isoxazole-4-carboxylic acid isobutylamide;
5-Methyl-isoxazole-4-carboxylic acid (n-pentyl)amide;
5-Methyl-isoxazole-4-carboxylic acid pyrrolidinehydrazide;
5-Methyl-isoxazole-4-carboxylic acid morpholinohydrazide;
5-Methyl-isoxazole-4-carboxylic acid 4-trifluoromethylbenzimide;
5-Methyl-isoxazole-4-carboxylic acid 2-fluoroethylamide;
5-Methyl-isoxazole-4-carboxylic acid *trans*-4-(tert-butylcyclohexyl)amide;
5-Methyl-isoxazole-4-carboxylic acid *cis*-4-(tert-butylcyclohexyl)amide;
5-Methyl-isoxazole-4-carboxylic acid diethylamide;
5-Methyl-isoxazole-4-carboxylic acid ethylamide;
5-Methyl-isoxazole-4-carboxylic acid 2,2,2-trifluoroethylamide;
5-Methyl-isoxazole-4-carboxylic acid allylamide;
5-Methyl-isoxazole-4-carboxylic acid propargylamide;
5-Methyl-isoxazole-4-carboxylic acid (acetonitrile)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-methoxyethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (3-methoxypropyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-diethoxyacetal)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-thioethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-hydroxyethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-hydroxybutyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-piperidinoethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-methylpiperazino)amide;
5-Methyl-isoxazole-4-carboxylic acid (ethylglycinate)amide;
5-Methyl-isoxazole-4-carboxylic acid (3-propionic acid)amide;
5-Methylisoxazole-4-carboxylic acid (1-piperidino)amide;
5-Methylisoxazole-4-carboxylic acid (4-chlorophenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-methylcyclohexyl)amide;

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5-Methyl-isoxazole-4-carboxylic acid (2-norbornyl)amide;
5-Methyl-4-{4-(3-trifluoromethylphenyl)piperazine-1-ylcarbonyl}-isoxazole;
5-Methyl-isoxazole-4-carboxylic acid (cyclobutylmethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (norephedrine)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-methoxycarbonylcyclohexylmethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-hydroxyphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-{(4-phenyl)-benzyl}amide;
5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-(4-phenoxy)-benzylamide;
5-Methyl-isoxazole-4-carboxylic acid {2-[(2-chloro-4-t-butyl-phenoxy)methyl]benzyl}amide;
5-Methyl-isoxazole-4-carboxylic acid (furfuryl)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-trifluoromethoxyphenyl)hydrazide ;
5-Methyl-isoxazole-4-carboxylic acid {(-)-*cis*-myrtanyl}amide;
5-Methyl-isoxazole-4-carboxylic acid (3-aminopropyl)amide;
5-Methylisoxazole-4-carboxylic acid (4-methoxyphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid {(4S)-benzyloxazolidinone}imide;
5-Methyl-isoxazole-4-carboxylic acid (4-methylphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid {(+)-norephedrine}amide;
5-Methyl-isoxazole-4-carboxylic acid (4-ethylphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid {2-hydroxy-5-(7-chloro-6-(ethoxycarbonylmethoxy)benzisoxazol-3-yl)benzyl}amide;
5-Methyl-isoxazole-4-carboxylic acid {4-(2,3-dichloro-4-(ethoxycarbonylmethoxy)benzoyl)benzyl}amide;
5-Methyl-isoxazole-4-carboxylic acid (aziridinyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-hydroxyphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-phenylethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid cinnamimide;
5-Methyl-isoxazole-4-carboxylic acid 4-chlorocinnamimide;
5-Methyl-isoxazole-4-carboxylic acid {L-(S)-amphetamine}amide;
5-(3-Butenyl) isoxazole-4-carboxylic acid (4-trifluoromethylphenyl)amide;
2-(4-Trifluoromethylphenyl)ethyl 5-methyl isoxazole-4-carboxylate;
2-(4-Nitrophenyl)ethyl 5-methyl-isoxazole-4-carboxylate;
2-(4-Fluorophenyl)ethyl 5-methyl-isoxazole-4-carboxylate;
4-Chlorophenethyl 5-methylisoxazole-4-carboxylate;
4-Trifluoromethylphenyl 5-methylisoxazole-4-carboxylate;
Cinnamyl 5-methylisoxazole-4-carboxylate;
2-(3-Trifluoromethylphenyl)ethyl 5-methylisoxazole-4-carboxylate;
3-Phenylbutyl 5-methylisoxazole-4-carboxylate;

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N[2-(4-Trifluoromethylphenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-(2-Phenylpropyl)-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Fluorophenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Nitrophenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-methoxycrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-ethoxycrotonamide;
N-[2-(4-Fluorophenyl)ethyl]-2-cyano-3-hydroxycrotonate;
N-[2-(4-Trifluoromethylphenyl)ethyl-2-cyano-3-hydroxycrotonate;
N-[n-Pentyl]-2-cyano-3-hydroxycrotonamide;
N-(Isobutyl)-2-cyano-3-hydroxycrotonamide;
N-(*trans*-4-tert-Butylcyclohexyl)-2-cyano-3-hydroxycrotonamide;
N-(*cis*-4-tert-Butyl cyclohexyl)-2-cyano-3-hydroxycrotonamide;
N-(2-Fluoroethyl)-2-cyano-3-hydroxycrotonamide;
N,N-Diethyl-2-cyano-3-hydroxycrotonamide;
N-Ethyl-2-cyano-3-hydroxycrotonamide;
N-(2,2,2-Trifluoroethyl)-2-cyano-3-hydroxycrotonamide;
N-[2(4-Nitrophenyl)ethyl]-2-cyano-3-hydroxycrotonate;
N-Benzyl-2-cyano-3-hydroxycrotonamide;
N-Allyl-2-cyano-3-hydroxycrotonamide;
N-(2-Methoxyethyl)-2-cyano-3-hydroxycrotonamide;
N-(3-Methoxypropyl)-2-cyano-3-hydroxycrotonamide;
N-Acetonitrile-2-cyano-3-hydroxycrotonamide;
N-Propargyl-2-cyano-3-hydroxycrotonamide;
N-(2-Hydroxyethyl)-2-cyano-3-hydroxycrotonamide;
N-(4-Hydroxybutyl)-2-cyano-3-hydroxycrotonamide;
4-Trifluoromethylphenyl-2-cyano-3-hydroxycrotonimide;
3-Phenyl-1-butyl-2-cyano-3-hydroxycrotonate;
N-(Acetic acid)-2-cyano-3-hydroxycrotonamide;
N-(2-Norbornyl)-2-cyano-3-hydroxycrotoamide;
N-(3-Propionic acid)-2-cyano-3-hydroxy-crotonamide;
N-[2-(4-Chlorophenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-(2-Piperidin-1-ylethyl)-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Chlorophenyl)ethyl]-2-cyano-3-hydroxycrotonate;
N-Cyclobutylmethyl-2-cyano-3-hydroxy crotonamide;
N-(Ethylglycinate)-2-cyano-3-hydroxycrotonamide;
Cinnamyl 2-cyano-3-hydroxycrotonate;
N-(Epi-4-Carboxycyclohexylmethyl)-2-Cyano-3-hydroxycrotonamide;

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N-(2-Methylcyclohexyl)-2-cyano-3-hydroxy crotonamide;
N-(2-Hydroxy-2-phenylethyl)-2-cyano-3-hydroxycrotonamide;
N-[2-(3-Trifluoromethylphenyl)ethyl]-2-cyano-3-hydroxycrotonate;
N-(Furfuryl)-2-cyano-3-hydroxy-crotonamide;
N-[2-(4-Methoxyphenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Methylphenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-((-)-cis-Myrtanyl)-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Ethylphenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
2-Cyano-3-hydroxy-crotonic acid aziridinyl amide;
N-[2-(4-Hydroxyphenyl)ethy]-2-cyano-3-hydroxycrotonamide;
2-Phenylethyl-2-cyano-3-hydroxycrotonamide;
2-Cyano-3-hydroxycrotonic 4-chlorocinnamimide;
2-Cyano-3-hydroxycrotonic cinnamimide;
(4(S)-Benzyl-2-oxazolidinone)-2-cyano-3-hydroxy-crotonimide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2',4'-dichlorophenyl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-phenylcrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4'-methoxyphenyl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4'-t-butylphenyl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(*trans*-phenylcyclopropyl)-acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-biphenyl-acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(3',4',5'-tri-methoxy-phenyl)-acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-phenylcrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4-trifluoromethylphenyl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(furan-2-yl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-5-phenyl-penta-2,4-dienoic acid amide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-methyl-penta-2,4-dienoic acid amide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-carboxyethylcrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-ethyl-oct-2-enoic acid amide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2-thienylmethyl)crotonamide; and
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-2,6-heptadieneamide

and the respective pharmaceutically acceptable salts, esters and prodrugs thereof.

In a further aspect of the present invention, pharmaceutical compositions are disclosed which comprise a therapeutically effective amount of a compound of the invention in combination with a pharmaceutically acceptable carrier.

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In yet another aspect of the present invention is disclosed a method of producing immunosuppression in a patient in need of such treatment, which comprises administering to the patient a therapeutically effective amount of a compound f the invention.

Detailed Description of the Invention

Preferred compounds of the present invention include those in which D is hydrogen or -C(O)R^9, where R^9 is as described above.

Also preferred are the compounds of the invention in which E is -$NR^{14}R^{15}$, -OR^{14} or -SR^{14}, and especially those where E is -$NR^{14}R^{15}$. Particularly preferred among these compounds are those in which R^{14} is X'-,Y'- and Z'-substituted aryl, heterocyclic, -heterocyclic-aryl or -aryl-heterocyclic, and those in which R^{15} is hydrogen, -(C_1-to-C_6 alkyl) or -(C_1-to-C_6 haloalkyl). Other preferred compounds of the invention include those compounds in which G is hydrogen, -(C_1-to-C_6 alkyl), -(C_1-to-C_6 haloalkyl) or X-, Y- and Z-substituted phenyl, and especially where G is methyl.

As used above and throughout this specification and in the appended claims, the following terms have the meanings specified:

The term "acyl" as used herein refers to a carbonyl group to which is appended an alkyl, heterocyclic or aryl residue where aryl, heterocyclic and alkyl have the definitions specified below.

The terms "alkenyl" and "loweralkenyl" as used herein refer to a branched or straight chain comprising two to ten carbon atoms which also comprises one or more carbon-carbon double bonds.

The terms "alkoxy" and "loweralkoxy" as used herein refer to a loweralkyl group, as defined below, attached to the remainder of the molecule through an oxygen atom. Alkoxy and loweralkoxy groups include, for example, methoxy, ethoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, isobutoxy, *tert*-butoxy and the like.

The term "alkoxycarbonyl" as used herein refers to an alkoxy group, as previously defined, attached to the parent molecular moiety through a carbonyl, -C(O)-. Alkoxycarbonyl includes, but is not limited to, ethoxycarbonyl, methoxycarbonyl, isopropoxycarbonyl and the like.

The term "alkyl" as used herein refers to a monovalent straight chain or branched chain group of one to twelve carbon atoms including, but not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl and the like.

The terms "alkylamino" and "loweralkylamino" as used herein refers to a group having the structure -NH-(loweralkyl), where the loweralkyl portion is as defined below. Alkylamino and loweralkylamino groups include, for example, methylamino, ethylamino, isopropylamino and the like.

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The term "amidoalkyl" as used herein refers to a group having the structure $-NR^{101}C(O)R^{102}$ appended t a loweralkyl group, as previously defined. The groups R^{101} and R^{102} are independently selected from hydrogen, lower alkyl, aryl, arylalkyl, and halosubstituted alkyl. Additionally, R^{101} and R^{102}, taken together, may optionally be $-(CH_2)_{aa}-$ where aa is an integer of from two to six.

The term "aminoalkyl" as used herein refers to a group having the structure $-NR^{103}R^{104}$ appended to a loweralkyl group, as previously defined. The groups R^{103} and R^{104} are independently selected from hydrogen, lower alkyl, aryl and arylalkyl. Additionally, R^{103} and R^{104}, taken together, may optionally be $-(CH_2)_{bb}-$ where bb is an integer of from two to six.

The term "aryl" as used herein refers to substituted and unsubstituted carbocyclic aromatic groups including, but not limited to, phenyl, 1- or 2-naphthyl, fluorenyl, (1,2)-dihydronaphthyl, (1,2,3,4)-tetrahydronaphthyl, indenyl, indanyl and the like, optionally substituted with 1, 2 or 3 substituents independently selected from halo, nitro, cyano, C_1 to C_{12} alkyl, alkoxy and halosubstituted alkyl.

The term "arylalkyl" as used herein refers to an aryl group, as previously defined, appended to an alkyl group including, but not limited to, benzyl, 1- and 2-naphthylmethyl, halobenzyl, alkoxybenzyl, hydroxybenzyl, aminobenzyl, nitrobenzyl, guanidinobenzyl, fluorenylmethyl, phenylmethyl(benzyl), 1-phenylethyl, 2-phenylethyl, 1-naphthylethyl and the like.

The term "arylalkoxy" as used herein refers to an arylalkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom. Arylalkoxy includes, but is not limited to, benzyloxy, 2-phenethyloxy, 1-naphthylmethyloxy and the like.

The term "arylalkoxycarbonyl" as used herein refers to an arylalkyl group, as previously defined, attached to the parent molecular moiety through a carbonyl group, -C(O)-. Arylalkoxycarbonyl includes, but is not limited to, benzyloxycarbonyl, 2-phenethyloxycarbonyl, 1-naphthylmethyloxycarbonyl and the like.

The term "arylalkylamino" as used herein refers to a group having the structure $-NR^{103}$-(arylalkyl), where the arylalkyl portion is as previously defined. Examples of arylalkylamino groups include benzylamino, 1-phenylethylamino and the like.

The term "aryloxy" as used herein refers to an aryl group, as previously defined, attached to the parent molecular moiety through an oxygen atom. Aryloxy includes, but is not limited to, phenoxy, 1-naphthoxy, 2-naphthoxy and the like.

The term "aryloxycarbonyl" as used herein refers to an aryloxy group, as previously defined, attached to the parent molecular moiety through a carbonyl group, -C(O)-.

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Aryloxycarbonyl includes, but is not limited to, phenoxycarbonyl, 1-naphthoxycarbonyl, 2-naphthoxycarbonyl and the like.

The term "arylsulfonyl" as used herein refers to an aryl group, as previ usly defined, attached to the parent molecular moiety through a sulfonyl group, $-S(O)_2-$. Arylsulfonyl includes, but is not limited to, benzenesulfonyl, 1- or 2-naphthylsulfonyl and the like.

The term "biaryl" as used herein refers to a group where two substituted or unsubstituted aryl groups as defined above are directly bound to each other including, but not limited to, biphenyl, 1-phenyl naphthyl, and the like.

The term "bicycloalkyl" as used herein refers to a ring system comprised of two fused cycloalkyl groups as defined below, including, but not limited to, norbornyl, norbornenyl and pinenyl.

The term "(bicycloalkyl)alkyl" as used herein refers to a bicycloalkyl group as defined above appended to a lower alkyl group including, but not limited to, norbornylmethyl and pinenylethyl.

The term "carboxyalkyl" as used herein refers to a carboxyl group, $-CO_2H$, appended to a loweralkyl group, as previously defined.

The term "cycloalkyl" as used herein refers to cyclic groups of three to eight carbons including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "(cycloalkyl)alkyl" as used herein refers to a cycloalkyl group appended to a lower alkyl group including, but not limited to, cyclohexylmethyl and cyclohexylethyl.

The term "guanidinoalkyl" as used herein refers to a group of the structure $-NR^{105}C(=NR^{106})NHR^{107}$ appended to a loweralkyl group, as previously defined. The substituents R^{105}, R^{106} and R^{107} are independently selected from hydrogen, lower alkyl, heterocyclic, aminoalkyl and aryl. Alternatively, R^{106}, and R^{107}, taken together, may optionally be $-(CH_2)_{cc}-$ wherein cc is an integer of from two to six.

The terms "halo" and "halogen" as used herein refer to an atom selected from fluorine, chlorine, bromine and iodine.

The term "haloalkyl" as used herein refers to alkyl groups as defined above containing one or more halogen atoms including, but not limited to, trifluoromethyl, 1,1-dichloroethyl, 1,1-difluoro-2,2-dichloroethyl, and the like.

The term "heterocyclic" as used herein, except where otherwise specified, refers to any aromatic or non-aromatic 5-, 6- or 7-membered ring or a bi- or tricyclic group comprising fused five, six or seven-membered rings having between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein (i) each 5-membered ring has 0 to 2 double bonds and each 6-membered ring has 0 to 3 double bonds, (ii) the nitrogen and sulfur heteroat ms as well as the carbon atoms may optionally be oxidized by unsaturation and/or introduction of hydroxy, thiol, oxo, thiooxo, (iii) the

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nitrogen heteroatom may optionally be quaternized, (iv) any of the above heterocyclic rings may be fused to a benzene ring, and (v) Any carbon or heteroatom with suitable valence may bear a substituent. Representative heterocycles include, but are not limited to, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, cytosinyl, thiocytosinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, xanthenyl, xanthonyl, xanthopterinyl, oxazoyl, oxazolidinyl, thiouracilyl, isoxazolyl, isoxazolidinyl, morpholinyl, indolyl, quinolinyl, uracilyl, urazolyl, uricyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, isoquinolinyl, thyminyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl and benzothienyl.

The terms "hydroxyalkyl" and "hydroxyloweralkyl" as used herein refer to -OH appended to a loweralkyl group, as defined below.

The term "hydroxy-protecting group" as used herein refers to those groups which are known in the art to protect a hydroxyl group against undesirable reaction during synthetic procedures and to be selectively removable including, but not limited to, methylthiomethyl, *tert*-dimethylsilyl, *tert*-butyldiphenylsilyl, acyl substituted with an aromatic group and other groups found in *Protective Groups in Organic Synthesis*, 2nd Ed., Greene, T.W. John Wiley & Sons, New York, 1991.

The term "loweralkyl" as used herein refers to an alkyl group, as defined above, of one to eight carbon atoms.

The terms "thioalkoxy" and "thioloweralkoxy" as used herein refer to a loweralkyl group, as previously defined, attached to the remainder of the molecule through a sulfur atom. Examples of thioalkoxy and thioloweralkoxy groups include, but are not limited to, thiomethoxy, thioethoxy, thioisopropoxy, *n*-thiobutoxy, *s*-thiobutoxy, isothiobutoxy, *t*-thiobutoxy and the like.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group, as defined above, appended to a loweralkyl group.

The term "thioarylalkoxy" as used herein refers to an arylalkyl group, as previously defined, attached to the remainder of the molecule through a sulfur atom.

The term "thioaryloxy" as used herein refers to an aryl group, as defined above, attached to the remainder of the molecule through a sulfur atom.

The term "pharmaceutically acceptable salts, esters, amides and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the

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relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable rganic r inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate and laurylsulphonate salts and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium and the like, as well as nontoxic ammonium, quaternary ammonium and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like. (See, for example S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 66:1-19 (1977) which is incorporated herein by reference.)

Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C_1 to C_6 alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5-to-C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C_1-to-C_4 alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C_1-to-C_6 alkyl amines and secondary C_1-to-C_6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5 or 6 membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1-to-C_3 alkyl primary amides and C_1-to -C_2 dialkyl secondary amides are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both f which are incorporated herein by reference.

Where appropriate, prodrugs of derivatives of compounds of the present invention may be prepared by any suitable method. For those compounds in which the prodrug moiety is an amino acid or peptide functionality, the condensation of the amino group with amino acids and peptides may be effected in accordance with conventional condensation methods such as the azide method, the mixed acid anhydride method, the DCC

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(dicyclohexylcarbodiimede) method, the active ester method (*p* -nitrophenyl ester method, N-hydroxysuccinic acid imide ester method, cyanomethyl ester method and the like), the Woodward reagent K method, the DCC-HOBT (1-hydroxy-benzotriazole) method and the like. Classical methods for amino acid condensation reactions are described in "Peptide Synthesis" Second Edition, M. Bodansky, Y.S. Klausner and M.A. Ondetti (1976).

Numerous asymmetric centers may exist in the compounds of the present invention. Except where otherwise noted, the present invention contemplates the various stereoisomers and mixtures thereof. Accordingly, whenever a bond is represented by a wavy line, it is intended that both steric orientations are intended.

The compounds of the invention, including but not limited to those specified in the examples, possess immunomodulatory activity in animals. As immunosuppressants, the compounds are expected to be useful in the treatment and/or prevention of rejection of transplanted organs or tissues, such as kidney, heart, lung, bone marrow, skin or cornea transplants, and also in the treatment or prevention of autoimmune, inflammatory, proliferative, and hyperproliferative diseases, such as rheumatoid arthritis, lupus erythematosus, sytemic lupus erythematosus, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, Hashimoto's thyroiditis, nephrotic syndrome, psoriasis, atopical dermatitis, contact dermatitis, seborrheic dermatitis, graft-versus-host diseases by medulla ossium transplantation, vernal keratocojunctivitis, eczematous dermatises, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, alopecia areata and the like.

The compounds of this invention are also expected to find use in the treatment of reversible obstructive airways disease. Further, the compounds of this invention may be indicated in the treatment of diseases caused by intestinal inflammations and allergies, such as Coeliac disease, gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, and the like; and food-related allergic diseases which have symptoms remote from the gastrointestinal tract, as for example migraine, rhinitis, and eczema.

Aqueous liquid compositions of the present invention may be particularly useful for the treatment and prevention of various diseases of the eye such as autoimmune diseases (including, for example, conical cornea, keratitis, dysophia epithelialis corneae, leukoma, Mooren's ulcer, sclevitis and Graves' ophthalmopathy) and rejection of corneal transplantation.

When used in the above or other treatments, a therapeutically effective amount of one of the compounds of the present invention may be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester or prodrug form. Alternatively, the compound may be administered as pharmaceutical compositions containing the compound of

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interest in combination with one or more pharmaceutically acceptable excipients. By a "therapeutically effective amount" of the compound of the invention is meant a sufficient amount of the compound to treat gastrointestinal disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required for to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The pharmaceutical compositions of the present invention comprise a compound of the invention and a pharmaceutically acceptable carrier or excipient, which may be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, or as an oral or nasal spray. By "pharmaceutically acceptable carrier" is meant a non-toxic solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection include pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusi n of various antibacterial and antifungal agents, for example,

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paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like, Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides) Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

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The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

Topical administration includes administration to the skin or mucosa, including surfaces of the lung and eye. Compositions for topical administration, including those for inhalation, may be prepared as a dry powder which may be pressurized or non-pressurized. In non-pressurized powder compositions, the active ingredient in finely divided form may be used in admixture with a larger-sized pharmaceutically acceptable inert carrier comprising particles having a size, for example, of up to 100 micrometers in diameter. Suitable inert carriers include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

Alternatively, the composition may be pressurized and contain a compressed gas, such as nitrogen or a liquified gas propellant. The liquified propellant medium and indeed the total composition is preferably such that the active ingredient does not dissolve therein to any substantial extent. The pressurized composition may also contain a surface active agent. The surface active agent may be a liquid or solid non-ionic surface active agent or may be a solid

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anionic surface active agent. It is preferred to use the solid anionic surface active agent in the form of a sodium salt.

A further form of topical administration is to the eye, as for the treatment of immune-mediated conditions of the eye such as automimmune diseases, allergic or inflammatory conditions, and corneal transplants. The compound of the invention is delivered in a pharmaceutically acceptable ophthalmic vehicle, such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye, as for example the anterior chamber, posterior chamber, vitreous body, aqueous humor, vitreous humor, cornea, iris/cilary, lens, choroid/retina and sclera. The pharmaceutically acceptable ophthalmic vehicle may, for example, be an ointment, vegetable oil or an encapsulating material.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq*.

One or more of the processes discussed below may be then employed to produce the desired compound of the invention. The compounds where E is $-NR^{14}R^{15}$ or $-OR^{14}$ may be prepared via condensation of the corresponding isoxazole-4-carboxylic acid or activated derivative with commercially available amines or alcohols thereby providing the respective amide or ester analogs. Many of these materials are prepared from the corresponding isoxazole acid chloride with two equivalents of amine or with an alcohol and a base used as an acid scavenger. Isoxazole-4-carboxylic acids are prepared from commercially available β-dicarbonyl compounds according to published methods involving homologation of the active methylene followed by hydroxylamine-mediated cyclization (Schenone *et al.* J. Het. Chem. 28 453-457 (1991) and Doleschall *et al.* J. Chem. Soc., Perkin Trans. I 1875-1879 (1988), incorporated herein by reference).

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Those analogs where E is $-CR^{14}R^{15}R^{16}$ are made using the previously detailed isoxazole synthesis using a β-diketone as the starting material.

Cleavage of the isoxazoles (I) to ring opened analogues (II) may be routinely done using an excess f aqueous sodium hydroxide in a hydroxylic solvent such as methyl or ethyl alcohol at temperatures ranging from ambient to reflux. The resulting hydroxycyanoacrylic acid derivatives are then purified, as for example via recrystallization or flash chromatography.

Representative of the processes of the invention is reaction Scheme I presented below. In Scheme I, a β-dicarbonyl compound 1 is reacted with a trialkylorthoformate such as triethylorthoformate in acetic anhydride to give the alkoxymethylene-dicarbonyl compound 2. Treatment of 2 with hydroxylamine hydrochloride in an alcoholic solution gives the isoxazole carboxylic acid ethyl ester 3. If necessary, the desired regioisomer is separated, and the purified ester is hydrolyzed under acidic conditions to give the carboxylic acid 4. The acid is activated, for example as the acid chloride 5 using thionyl chloride. Compound 5 is then reacted with the appropriate amines to give carboxamides 6 or the appropriate alcohols to give esters 7.

Analogously when the starting material is a β-diketone 8, rather than a β-ketoester, homologation of the α-methylene group gives the alkoxymethylenediketone 9, as shown in Scheme II. Cyclization with hydroxylamine hydrochloride gives the acyl isoxazole compound 10.

Scheme III shows the ring opening of the isoxazole with base, for example, sodium hydroxide in an alcoholic solution to give the hydroxycyanoacrylic acid derivative 12.

Alternatively, 12 can be prepared by reaction of the corresponding cyanoacetyl precursor 14 with activated acid derivatives (e.g. an acid chloride) 13.

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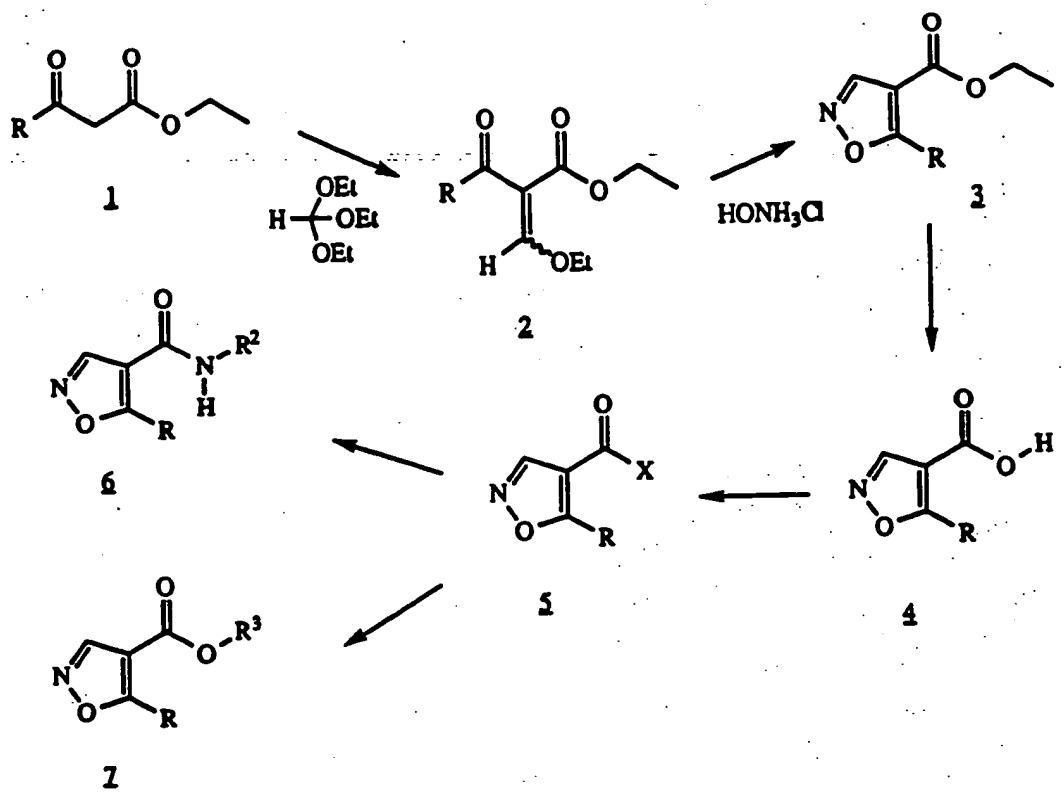
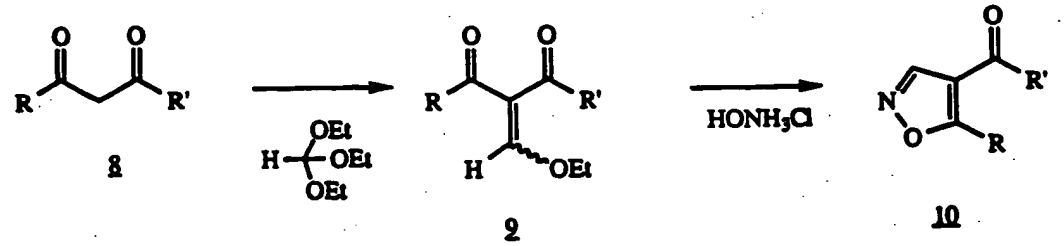
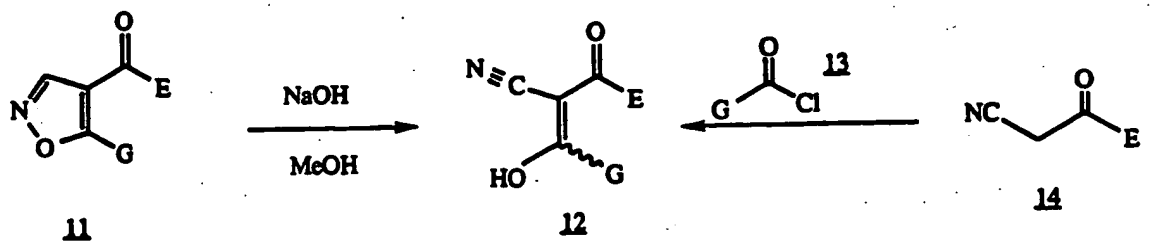
Scheme I



Scheme II



Scheme III



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The compounds, processes and uses of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention. Both below and throughout the specification, it is intended that citations to the literature are expressly incorporated by reference.

Example 1

5-Methyl-isoxazole-4-carboxylic acid 2-(4-trifluoromethylphenyl)ethylamide

Step A: 5-Methylisoxazole-4-carboxylic acid chloride

5-Methylisoxazole-4-carboxylic acid (prepared following the procedure of Schenone *et al*) (2.65 g, 20.8 mmol) and 10 mL of $SOCl_2$ were combined and stirred at reflux for 3 hours. The excess $SOCl_2$ was removed by distillation at atmospheric pressure. The residual acid chloride was purified via bulb-to-bulb distillation at high vacuum and ambient temperature thereby affording 2.71g of pure title compound.

Step B: 5-Methyl-isoxazole-4-carboxylic acid 2-(4-trifluoromethylphenyl)ethylamide:

To a solution of the compound resulting from Step A (310 mg, 2.14 mmol) in 5 mL of dry acetonitrile stirred at ambient temperature was added 4-trifluoromethylphenethyl amine (800 mg, 4.23 mmol) in 2 mL of acetonitrile dropwise. After stirring for 75 minutes, the reaction was filtered and the collected precipitate was washed with acetonitrile (2x50 mL). The combined filtrates were concentrated *in vacuo* and the residual crude amide was purified by recrystallization from toluene and overnight vacuum drying. m.p. 93°C. Anal calcd for $C_{14}H_{13}N_2O_2F_3$: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.41; H, 4.37; N, 9.18.

Examples 2-64

Following the procedures described in Example 1 but substituting in each case the appropriate amine reagent for the 4-trifluoromethylphenethyl amine of Step B, the following amide derivatives were prepared:

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Ex. #	Name	MP (°C)	% C Calcd	% H Calcd	% N Calcd	% C Found	% H Found	% N Found
2	3,5-Dimethylisoxazole-4-carboxylic acid 2-(trifluoromethylphenyl)ethyl-amide	181	-	-	-	-	-	-
3	3,5-Dimethylisoxazole-4-carboxylic acid (4-fluorophenyl)amide	156-7	-	-	-	-	-	-
4	5-Methyl-isoxazole-4-carboxylic acid 2-(4-fluorophenyl)ethylamide	78-80	62.90	5.28	11.28	62.82	5.26	11.26
5	5-Methyl-isoxazole-4-carboxylic acid 2-phenylpropylamide	88-92	68.83	6.60	11.47	68.77	6.57	11.51
6	5-Methyl-isoxazole-4-carboxylic acid 2-(4-nitrophenyl)ethylamide	139-141	56.73	4.76	15.27	56.77	4.85	15.05
7	5-Methyl-isoxazole-4-hydroxamic acid benzylamide	116-118	62.06	5.21	12.06	61.86	5.26	11.87
8	5-Methyl-isoxazole-4-carboxylic acid 4-fluorophenylhydrazide	146-148	56.17	4.29	17.86	55.93	4.32	17.53
9	5-Methyl-isoxazole-4-carboxylic acid (7-trifluoromethyl-1,2,3,4-tetrahydroquinolinyl)amide	oil	58.07	4.22	9.03	58.01	4.39	8.68

Example 9: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.89-2.0 (m, 2H), 2.34 (s,3H), 2.87 (t, J = 7.5Hz, 2H), 3.70 (t, J = 7.5Hz, 2H), 7.39-7.55 (m, 3H), 8.34 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 11.46, 22.9, 26.2, 44.5, 112.1, 120.8*, 129.6, 138.4, 149.8, 161.7, 170.3 (* indicates resonances with observed C-F couplings).

10	5-Methyl-isoxazole-4-carboxylic acid (6-methyl-1,2,3,4-tetrahydroquinolinyl)amide	100-102	70.29	6.29	10.93	70.56	6.30	10.93
11	5-Methyl-isoxazole-4-carboxylic acid isobutylamide	80-81	59.32	7.74	15.37	59.37	7.79	15.33
12	5-Methyl-isoxazole-4-carboxylic acid (n-pentyl)amide	61	61.20	8.21	14.27	61.32	8.12	14.62
13	5-Methyl-isoxazole-4-carboxylic acid pyrrolidinehydrazide	175-6	-	-	-	-	-	-
14	5-Methyl-isoxazole-4-carboxylic acid morpholinohydrazide	164	51.18	6.20	19.90	51.15	6.15	19.89
15	5-Methyl-isoxazole-4-carboxylic acid 4-trifluoromethylbenzimide	148-150	52.36	3.04	9.39	52.10	2.98	9.23
16	5-Methyl-isoxazole-4-carboxylic acid 2-fluoroethylamide	93-94	48.83	5.26	16.27	48.54	5.21	16.15
17	5-Methyl-isoxazole-4-carboxylic acid *trans*-4-(*t*-butylcyclohexyl)amide	98	68.15	9.15	10.60	68.17	9.16	10.51
18	5-Methyl-isoxazole-4-carboxylic acid *cis*-4-(*t*-butylcyclohexyl)amide	194-5	68.15	9.15	10.60	67.95	8.86	10.51
19	5-Methyl-isoxazole-4-carboxylic acid diethylamide	oil	59.32	7.74	15.37	58.38	7.87	14.66
20	5-Methyl-isoxazole-4-carboxylic acid ethylamide	99-100	54.53	6.53	18.17	54.50	6.52	18.01

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21	5-Methyl-isoxazole-4-carboxylic acid 2,2,2-trifluoroethylamide	133-134	40.39	3.38	13.45	40.40	3.30	13.24
22	5-Methyl-isoxazole-4-carboxylic acid allylamide	56-57	57.82	6.60	16.85	57.85	6.11	16.85
23	5-Methyl-isoxazole-4-carboxylic acid propargylamide	131-132	58.53	4.91	17.60	58.31	4.93	16.72
24	5-Methyl-isoxazole-4-carboxylic acid (acetonitrile)amide	95-96	50.90	4.27	25.44	50.87	4.33	25.26
25	5-Methyl-isoxazole-4-carboxylic acid (2-methoxyethyl)amide	68-69	52.16	6.56	15.20	52.16	6.64	15.31
26	5-Methyl-isoxazole-4-carboxylic acid (3-methoxypropyl)amide	50-51	54.53	7.11	14.13	54.40	7.16	14.06
27	5-Methyl-isoxazole-4-carboxylic acid (2-diethoxyacetal)amide	46-47	54.53	7.48	11.56	54.67	7.39	11.49
28	5-Methyl-isoxazole-4-carboxylic acid (2-thioethyl)amide	87-89	45.14	5.41	15.04	45.48	5.14	14.86
29	5-Methyl-isoxazole-4-carboxylic acid (2-hydroxyethyl)amide	112-114	49.40	5.92	16.46	49.33	5.99	16.41
30	5-Methyl-isoxazole-4-carboxylic acid (4-hydroxybutyl)amide	83	54.53	7.11	14.13	54.46	7.12	13.80
31	5-Methyl-isoxazole-4-carboxylic acid (2-piperidinoethyl)amide HCl	183-185	52.65	7.36	15.35	52.59	7.33	15.24
32	5-Methyl-isoxazole-4-carboxylic acid (4-methylpiperazino)amide HCl	185-187	46.07	6.57	21.49	45.99	6.46	21.56

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33	5-Methyl-isoxazole-4-carboxylic acid (ethylglycinate)amide	68-70	50.94	5.69	13.20	51.11	5.53	13.21
34	5-Methyl-isoxazole-4-carboxylic acid (3-propionic acid)amide	123-126	48.48	5.08	14.13	48.17	5.13	13.70
35	5-Methylisoxazole-4-carboxylic acid (1-piperidino)amide hydrochloride	154-156	48.88	6.56	17.10	48.55	6.46	17.33
36	5-Methylisoxazole-4-carboxylic acid (4-chlorophenethyl)amide	110-113	58.99	4.95	10.58	58.85	4.94	10.53
37	5-Methyl-isoxazole-4-carboxylic acid (2-methylcyclohexyl)amide	95-98	64.86	8.11	12.61	64.37	8.09	12.35
38	5-Methyl-isoxazole-4-carboxylic acid (2-norbornyl)amide	131-4	65.45	7.27	12.73	65.04	7.34	12.45
39	5-Methyl-4-{4-(3-trifluoromethylphenyl)piperazine-1-ylcarbonyl}-isoxazole HCl	165-170	51.14	4.56	11.18	51.05	4.52	11.22
40	5-Methyl-isoxazole-4-carboxylic acid (cyclobutylmethyl)amide	110-112	61.85	7.22	14.43	61.72	7.35	14.70
41	5-Methyl-isoxazole-4-carboxylic acid (norephedrine)amide	118-122	64.6	6.19	10.76	64.53	5.96	10.77
42	5-Methyl-isoxazole-4-carboxylic acid (4-methoxycarbonyl-cyclohexylmethyl)amide	95-97.0	60.00	7.14	10.00	60.33	7.09	9.95
43	5-Methyl-isoxazole-4-carboxylic acid (2-hydroxyphenethyl)amide	132-135	63.40	5.72	11.37	62.85	5.65	11.17

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44	5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-{(4-phenyl)-benzyl}amide		-	-	-	-	-	-
45	5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-(4-phenoxy)-benzylamide		-	-	-	-	-	-
46	5-Methyl-isoxazole-4-carboxylic acid {2-[(2-chloro-4-t-butyl-phenoxy)methyl]benzyl}amide	oil	-	-	-	-	-	-
47	5-Methyl-isoxazole-4-carboxylic acid (furfuryl)amide	92-93	58.24	4.88	13.58	58.41	4.84	13.52
48	5-Methyl-isoxazole-4-carboxylic acid (4-trifluoromethoxy-phenyl)hydrazide	126-128	47.85	3.35	13.95	47.92	3.23	13.90
49	5-Methyl-isoxazole-4-carboxylic acid {(-)-*cis*-myrtanyl}amide	107-109	68.67	8.45	10.67	68.63	8.20	10.69
50	5-Methyl-isoxazole-4-carboxylic acid (3-aminopropyl)amide hydrochloride	151-157	43.74	6.42	19.12	40.66	5.95	17.78
51	5-Methylisoxazole-4-carboxylic acid (4-methoxyphenethyl)amide	80-81	64.60	6.20	10.76	64.64	6.14	10.74
52	5-Methyl-isoxazole-4-carboxylic acid {(4S)-benzyl-oxazolidinone}imide	116-118	62.93	4.92	9.78	62.89	4.99	9.77
53	5-Methyl-isoxazole-4-carboxylic acid (4-methylphenethyl)amide	86-87	68.83	6.60	11.47	68.80	6.71	11.41
54	5-Methyl-isoxazole-4-carboxylic acid {(+)-norephedrine}amide	124-125	64.60	6.19	10.76	64.61	6.05	10.77

BNSDOCID: <WO__9424095A1_L>

55	5-Methyl-isoxazole-4-carboxylic acid (4-ethylphenethyl)amide	91-93	69.74	7.02	10.84	69.80	6.91	10.80
56	5-Methyl-isoxazole-4-carboxylic acid {2-hydroxy-5-(7-chloro-6-(ethoxycarbonylmethoxy)benzisoxazol-3-yl)benzyl}amide	138-40	-	-	-	-	-	-
57	5-Methyl-isoxazole-4-carboxylic acid {4-(2,3-dichloro-4-(ethoxycarbonylmethoxy)-benzoyl)benzyl}amide	98-101	-	-	-	-	-	-
58	5-Methyl-isoxazole-4-carboxylic acid (aziridinyl)amide	97-98	-	-	-	-	-	-
59	5-Methyl-isoxazole-4-carboxylic acid (4-hydroxyphenethyl)amide	133-135	63.40	5.73	11.38	63.38	5.87	11.31
60	5-Methyl-isoxazole-4-carboxylic acid (2-phenylethyl)amide	79-81	67.81	6.13	12.17	67.75	6.07	12.21
61	5-Methyl-isoxazole-4-carboxylic acid cinnamimide	184-186	65.62	4.72	10.93	66.02	4.95	10.90
62	5-Methyl-isoxazole-4-carboxylic acid 4-chlorocinnamimide	185-187	57.84	3.81	9.64	58.25	3.75	9.60
63	5-Methyl-isoxazole-4-carboxylic acid {L-(S)-amphetamine}amide	89-91	68.83	6.60	11.46	68.98	6.66	11.47
64	5-(3-Butenyl) isoxazole-4-carboxylic acid (4-trifluoromethylphenyl)amide	103	58.07	4.22	9.03	57.93	4.27	8.89

SUBSTITUTE SHEET (RULE 26)

Example 65

2-(4-Trifluoromethylphenyl)ethyl 5-methyl-isoxazole-4-carboxylate

To a solution of the compound resulting from Example 1 Step A (1.20 g, 8.24 mmol), in 12 mL of dry acetonitrile stirred at ambient temperature, was added 4-trifluoromethylphenethyl alcohol (3.04 g, 16 mmol) and pyridine (1.62 g, 20.5 mmol) in 10 mL of acetonitrile portionwise. The reaction was stirred for 8 hours and then 2N HCl was added. The resulting mixture was extracted with EtOAc and the combined organic extracts were washed with water and brine, dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* to afford crude product which was purified by flash chromatography on silica gel eluting with 40% EtOAc-heptane to afford the desired ester. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.57 (s, 3H), 3.11 (t, J = 6.5Hz, 2H), 4.48 (t, J = 6.5Hz, 2H), 7.5-7.7 (AA'BB', 4H), 8.81(s, 1H). ^{13}C NMR d 12.1, 33.9, 64.5, 108.9, 125.0*, 126.5*, 129.7, 130.1, 143.0, 150.3*, 160.1, 174.1 (* indicates resonances with observed C-F couplings).

Examples 66-72

Following the procedures described in Example 65 but substituting in each case the appropriate alcohol reagent for 4-trifluoromethylphenethyl alcohol, the following ester derivatives were similarly prepared:

BNSDOCID: <WO__9424095A1_I_>

Ex. #	Name	MP (°C)	% C Calcd	% H Calcd	% N Calcd	% C Found	% H Found	% N Found
66	2-(4-Nitrophenyl)ethyl 5-methyl-isoxazole-4-carboxylate	74-76	56.52	4.38	10.14	56.29	4.24	10.07
67	2-(4-Fluorophenyl)ethyl 5-methyl-isoxazole-4-carboxylate	40-42	62.65	4.85	5.62	62.81	4.84	5.59
68	4-Chlorophenethyl 5-methylisoxazole-4-carboxylate	73-74	58.77	4.55	5.27	58.81	4.51	5.28
69	4-Trifluoromethylphenyl 5-methylisoxazole-4-carboxylate	38-40	53.15	2.97	5.16	53.32	2.88	5.25
70	Cinnamyl 5-methylisoxazole-4-carboxylate	oil	69.12	5.39	5.76	69.15	5.48	5.53
71	2-(3-Trifluoromethylphenyl)ethyl 5-methylisoxazole-4-carboxylate	26-28	56.19	4.04	4.68	56.21	3.94	4.71
72	3-Phenylbutyl 5-methylisoxazole-4-carboxylate	oil	69.48	6.61	5.40	69.50	6.76	5.42

BNSDOCID: <WO__9424095A1_L>

Example 73

N-[2-(4-Trifluoromethylphenyl)ethyl]-2-cyano-3-hydroxycrotonamide

To the compound resulting from Example 1 (110 mg) in 10 mL of MeOH stirred at 25 °C was slowly added 10 mL of a 2 N NaOH solution . The reaction was then stirred at reflux for 3 hours followed by cooling to ambient temperature. Dilution with 50 mL of water followed by acidification with concentrated HCl afforded a precipitate. The collected solid was washed with water and recrystalized twice from EtOH to give the title compound. m.p. 177-178 °C. Anal calcd for $C_{14}H_{13}N_2O_2F_3$: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.48; H, 4.47; N, 9.02.

Examples 74-123

Following the procedures described in Example 73 but substituting in each case as starting material the product of the Example indicated below for the product of Example 1, the following metabolite derivatives were similarly prepared.

BNSDOCID: <WO___9424095A1_I_>

Ex. #	Name	Starting material Ex. #	MP (°C)	% C Calcd	% H Calcd	% N Calcd	% C Found	% H Found	% N Found
74	N-(2-Phenylpropyl)-2-cyano-3-hydroxycrotonamide	5	73-74	68.83	6.60	11.47	68.70	6.56	11.38
75	N-[2-(4-Fluorophenyl)ethyl]-2-cyano-3-hydroxycrotonamide	4	151-153	62.90	5.28	11.28	62.98	5.28	11.29
76	N-[2-(4-Nitrophenyl)ethyl]-2-cyano-3-hydroxycrotonamide	6	171-173	56.73	4.76	15.27	51.04	4.28	13.71
77	N-(4-Trifluoromethylphenyl)-2-cyano-3-methoxycrotonamide	NA	174	54.93	3.90	9.86	55.05	3.86	9.80
78	N-(4-Trifluoromethylphenyl)-2-cyano-3-ethoxycrotonamide	NA	138	56.38	4.39	9.39	56.23	4.30	9.40
79	N-[2-(4-Fluorophenyl)ethyl]-2-cyano-3-hydroxycrotonate	67	82-84	62.65	4.85	5.62	62.81	4.92	5.61
80	N-[2-(4-Trifluoromethylphenyl)-ethyl-2-cyano-3-hydroxycrotonate	65	110-112	56.19	4.04	4.68	55.94	4.05	4.56
81	N-[n-Pentyl]-2-cyano-3-hydroxycrotonamide	12	57	61.20	8.21	14.27	61.24	8.32	14.22
82	N-(Isobutyl)-2-cyano-3-hydroxycrotonamide	11	105-106	59.32	7.74	15.37	59.31	7.79	15.22
83	N-(*trans*-4-tert-butylcyclohexyl)-2-cyano-3-hydroxycrotonamide	17	155-6	68.14	9.15	10.60	68.17	9.08	10.58

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84	N-(*cis*-4-tert-butyl cyclohexyl)-2-cyano-3-hydroxycrotonamide	18	139	68.14	9.15	10.60	68.13	9.15	10.52
85	N-(2-Fluoroethyl)-2-cyano-3-hydroxycrotonamide	16	92-93	48.83	5.26	16.27	48.73	5.24	16.13
86	N,N-Diethyl-2-cyano-3-hydroxycrotonamide	19	oil	59.32	7.74	15.37	59.17	7.72	15.17
87	N-Ethyl-2-cyano-3-hydroxycrotonamide	20	88	54.53	6.53	18.17	54.21	6.53	18.06
88	N-(2,2,2-Trifluoroethyl)-2-cyano-3-hydroxycrotonamide	21	170-171	40.39	3.38	13.45	39.97	3.29	13.35
89	N-[2-(4-Nitrophenyl)ethyl]-2-cyano-3-hydroxycrotonate	66	120-121	56.52	4.38	10.14	56.88	4.50	10.17
90	N-Benzyl-2-cyano-3-hydroxycrotonamide	NA		66.65	5.59	12.95	66.41	5.60	12.82
91	N-Allyl-2-cyano-3-hydroxycrotonamide	22	99-100	57.82	6.06	16.85	57.60	6.00	16.75
92	N-(2-Methoxyethyl)-2-cyano-3-hydroxycrotonamide	25	62-64	52.16	6.56	15.20	52.35	6.51	15.11
93	N-(3-Methoxypropyl)-2-cyano-3-hydroxycrotonamide	26	38-39	54.53	7.11	14.13	54.58	7.04	14.01
94	N-Acetonitrile-2-cyano-3-hydroxycrotonamide	24	167-168 (dec)	50.90	4.27	25.44	50.94	4.11	25.16
95	N-Propargyl-2-cyano-3-hydroxycrotonamide	23	126	58.53	4.91	17.06	58.55	4.83	17.10
96	N-(2-Hydroxyethyl)-2-cyano-3-hydroxycrotonamide	29	96-97	49.4	5.92	16.46	49.46	5.82	16.45

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97	N-(4-Hydroxybutyl)-2-cyano-3-hydroxycrotonamide	30	84-85	54.53	7.11	14.13	54.64	7.08	13.99
98	4-Trifluoromethylphenyl-2-cyano-3-hydroxycrotonimide Triethylamine salt	15	101-103	57.14	6.06	10.52	57.12	5.96	10.50
99	3-Phenyl-1-butyl-2-cyano-3-hydroxycrotonate	72	119-125	69.48	6.61	5.40	66.25	6.13	5.07
100	N-(Acetic acid)-2-cyano-3-hydroxycrotonamide	NA	148-149	45.65	4.37	15.21	45.75	4.32	15.06
101	N-(2-Norbornyl)-2-cyano-3-hydroxycrotoamide	38	93-6	65.45	7.27	12.73	65.69	7.25	12.78
102	N-(3-Propionic acid)-2-cyano-3-hydroxy-crotonamide	34	142-144	48.48	5.08	14.13	48.53	4.94	13.85
103	N-[2-(4-Chlorophenyl)ethyl]-2-cyano-3-hydroxycrotonamide	36	171-173	58.99	4.95	10.58	58.87	4.80	10.51
104	N-(2-Piperidin-1-ylethyl)-2-cyano-3-hydroxycrotonamide • Trifluoroacetate salt	31	79-85	47.86	5.74	11.96	46.03	5.27	11.40
105	N-[2-(4-Chlorophenyl)ethyl]-2-cyano-3-hydroxycrotonate	68	75-77	58.77	4.55	5.27	58.87	4.40	5.27
106	N-Cyclobutylmethyl-2-cyano-3-hydroxy crotonamide	40	105-107	61.85	7.22	14.43	61.95	7.13	14.44
107	N-(Ethylglycinate)-2-cyano-3-hydroxycrotonamide	33	122-123	50.94	5.96	13.20	50.78	5.61	13.20
108	Cinnamyl 2-cyano-3-hydroxycrotonate	70	101-103	69.12	5.39	5.76	68.91	5.38	5.76

109	N-(Epi-4-Carboxycyclohexylmethyl)-2-cyano-3-hydroxycrotonamide	42	192-195	58.65	6.77	10.53	59.00	6.83	10.55
110	N-(2-Methylcyclohexyl)-2-cyano-3-hydroxy crotonamide	37	117-120	64.86	8.11	12.61	64.87	8.08	12.61
111	N-(2-Hydroxy-2-phenylethyl)-2-cyano-3-hydroxycrotonamide	43	117-118	63.40	5.72	11.37	63.28	5.81	11.28
112	N-[2-(3-Trifluoromethylphenyl)ethyl]-2-cyano-3-hydroxycrotonate	71	73-83	56.19	4.04	4.68	52.06	3.60	4.37
113	N-(Furfuryl)-2-cyano-3-hydroxy-crotonamide	47	108-109	58.24	4.88	13.58	58.03	4.99	13.45
114	N-[2-(4-Methoxyphenyl)ethyl]-2-cyano-3-hydroxycrotonamide	51	131-133	64.60	6.20	10.76	64.51	6.10	10.72
115	N-[2-(4-Methylphenyl)ethyl]-2-cyano-3-hydroxycrotonamide	53	139-141	68.83	6.60	11.47	69.17	6.63	11.53
116	N-((-)-cis-Myrtanyl)-2-cyano-3-hydroxycrotonamide	49	81-83	68.67	8.45	10.67	68.67	8.25	10.71
117	N-[2-(4-Ethylphenyl)ethy]-2-cyano-3-hydroxycrotonamide	55	126-127	69.74	7.02	10.84	69.71	7.10	10.83
118	2-Cyano-3-hydroxy-crotonic acid aziridinyl amide	58	115-116	55.25	5.29	18.41	39.34	4.02	12.99
119	N-[2-(4-Hydroxyphenyl)ethy]-2-cyano-3-hydroxycrotonamide	59	151-153	63.40	5.73	11.38	63.18	5.74	11.38
120	2-Phenylethyl-2-cyano-3-hydroxycrotonamide	60	133-135	67.81	6.13	12.17	67.81	5.99	12.12

121	2-Cyano-3-hydroxycrotonic 4-chlorocinnaminide triethylamine salt	62	143-145	61.30	6.69	10.72	61.28	6.65	10.61		
122	2-Cyano-3-hydroxycrotonic cinnamimide triethylamine salt	61	116-118	67.20	7.61	11.76	66.98	7.34	11.64		
123	(4(S)-Benzyl-2-oxazolidinone)-2-cyano-3-hydroxy-crotonimide	52	128-130	62.93	4.92	9.78	62.70	4.83	9.72		

BNSDOCID: <WO___9424095A1_I_>

Example 124-139

The following compounds were prepared by the reaction of the corresponding cyanoacetyl precursor with an activated acid derivative, such as an acid chloride, as depicted in scheme III.

BNSDOCID: <WO__9424095A1_I_>

Ex. #	Name	MP (°C)	% C Calcd	% H Calcd	% N Calcd	% C Found	% H Found	% N Found
124	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2',4'-dichlorophenyl)acrylamide	187-188	50.90	2.26	6.98	50.85	2.30	6.97
125	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-phenylcrotonamide	244-246	61.45	3.33	8.43	61.26	3.33	8.40
126	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4'-methoxyphenyl)acrylamide	260-262	59.67	3.61	7.73	59.75	3.51	7.69
127	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4'-t-butylphenyl)acrylamide	251-252	64.94	4.93	7.21	65.25	4.99	7.22
128	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(*trans*-phenylcyclopropyl)-acrylamide	200-202	64.51	4.06	7.52	64.88	3.93	7.57
129	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-biphenyl-acrylamide	272-274	67.64	3.70	6.85	67.78	3.59	6.89
130	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(3',4',5'-tri-methoxy-phenyl)-acrylamide	185-186	56.87	4.05	6.63	56.80	4.09	6.63

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131	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-phenylcrotonamide	163-165	62.42	3.78	8.08	62.27	3.85	8.18
132	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4-trifluoromethylphenyl)acrylamide	231-232	54.01	2.51	6.99	53.69	2.50	-
133	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(furan-2-yl)acrylamide	255-257	55.90	2.81	8.69	56.08	2.77	8.78
134	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-5-phenyl-penta-2,4-dienoic acid amide	259-261	63.68	3.65	7.81	63.67	3.53	7.78
135	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-methyl-penta-2,4-dienoic acid amide	192-194	56.76	3.74	9.45	56.73	3.65	9.45
136	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-carboxyethylcrotonamide	190-191	52.63	3.82	8.18	52.67	3.85	8.18
137	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-ethyl-oct-2-enoic acid amide	107-108	61.01	5.97	7.91	60.96	5.87	7.87
138	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2-thienylmethyl)crotonamide	155	54.54	3.15	7.95	54.64	3.12	7.94

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139	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-2,6-heptadieneamide	158-66	58.07	4.22	9.03	58.04	4.18	8.77

BNSDOCID: <WO___9424095A1_I_>

Examples 140-172

Following the procedures described in Example 1 but substituting in each case the appropriate amine reagent for the 4-trifluoromethylphenethyl amine of Step B, the following amide derivatives may be prepared:

Ex. #	Name
140	5-Methyl-isoxazole-4-carboxylic acid cycloleucinolamide;
141	5-Methyl-isoxazole-4-carboxylic acid (tyrosine methyl ester)amide;
142	5-Methyl-isoxazole-4-carboxylic acid 1-aminohomopiperidinehydrazide;
143	5-Methyl-isoxazole-4-carboxylic acid (2-amino-2-norbornanecarboxylic acid)amide;
144	5-Methyl-isoxazole-4-carboxylic acid 2-thienylmethylamide;
145	5-Methyl-isoxazole-4-carboxylic acid (2,6-dimethylmorpholine)amide;
146	5-Methyl-isoxazole-4-carboxylic acid 2-(N,N-dimethylamino)ethylamide;
147	5-Methyl-isoxazole-4-carboxylic acid 2-cyclohex-1-enylethylamide;
148	5-Methyl-isoxazole-4-carboxylic acid N-benzyl-N-norbornylamide;
149	5-Methyl-isoxazole-4-carboxylic acid (convolvinyl)amide;
150	5-Methyl-isoxazole-4-carboxylic acid 4-propylpiperidineamide;
151	5-Methyl-isoxazole-4-carboxylic acid {4-[(4-hydroxy-3-*t*-butyl)-phenoxyethoxy]phenyl}amide;
152	5-Methyl-isoxazole-4-carboxylic acid 4-[2-(phenylaminocarbonyl)-propionyl]anilide;
153	5-Trifluoromethyl-isoxazole-4-carboxylic acid 3-methyl-1-butylamide;
154	5-Methyl-isoxazole-4-carboxylic acid 5-(1-morpholino)amylamide;
155	5-Methyl-isoxazole-4-carboxylic acid (5-diisopropylamino-1,3,4-thiadiazol-2-yl)amide;
156	5-Methyl-isoxazole-4-carboxylic acid (L-proline tert-butyl ester)amide;
157	5-Methyl-isoxazole-4-carboxylic acid (L-leucine tert-butyl ester)amide;
158	5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-(1-cyano)cyclopentanylamide;
159	5-Methyl-isoxazole-4-carboxylic acid N-ethyl-N-(1-carboxyl)cycloheptylamide;
160	5-Methyl-isoxazole-4-carboxylic acid 4-[2-(2-methoxyethoxy)ethoxy]anilide;
161	5-Methyl-isoxazole-4-carboxylic acid (glycine trityl ester)amide;

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162 5-Methyl-isoxazole-4-carboxylic acid (ketamine hydrochloride)amide;
163 5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-(5,6-dehydro-exo-2-norbornyl)amide;
164 5-Methyl-isoxazole-4-carboxylic acid (β-alanine *t*-butyl ester)amide;
165 4-Trifluoromethylbenzoyl 5-trifluoromethyl-isoxazole-4-carboximide
166 3-(3-Methoxy)phenoxycarbonyl-5-methyl-isoxazole-4-carboxylic acid 3-methylbutylamide;
167 3-(N,N-Dimethylaminocarbonyl)-5-methyl-isoxazole-4-carboxylic acid 3-(4-methoxyphenyl)propylamide;
168 3-(2-Chloro-4-fluorophenacyl)-5-methyl-isoxazole-4-carboxylic acid cyclohexylamide;
169 N-(5-Phenyl-4-isoxazoyl)-N'-(4-toluenesulfonyl) 1,4 phenylenediamide;
170 5-Phenyl-isoxazole-4-carboxylic acid butylamide;
171 5-Trifluoromethyl-isoxazole-4-carboxylic acid (3-methylbutyl)amide; and
172 5-(2-Methoxyphenyl)-isoxazole-4-carboxylic acid 4-(3-nitrophenyl)thiazol-2-ylamide.

Examples 173-179

Following the procedures described in Example 65 but substituting in each case the appropriate alcohol reagent for 4-trifluoromethylphenethyl alcohol, the following ester derivatives may be prepared:

Ex. #	Name
173	(3-Furanyl)methyl 5-methyl-isoxazole-4-carboxylate;
174	2-(1-Piperidyl)ethyl 5-methyl-isoxazole-4-carboxylate;
175	3-Pyridyl 5-methyl-isoxazole-4-carboxylate;
176	4-[2-Methyl-5-(4-nitrophenyl)oxazolyl]methyl 5-methyl-isoxazole-4-carboxylate;
177	7-Chloro-4-quinolyl 5-methyl-isoxazole-4-carboxylate;
178	2-Methoxyethyl 5-(4-nitrophenyl)isoxazole-4-carboxylate; and
179	2-(4-Nitrophenyl)ethyl 5-trifluoromethylisoxazole-4-carboxylate.

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Example 180

3-Hydroxypropyl (5-phenyl-4-isoxazolyl) ketone

H mologation of the α-methylene group of 1-hydroxy-6-phenylhexane-4,6-di ne with triethylorthoformate followed by cyclization with hydroxylamine hydrochloride as depicted in scheme II and described in Schenone *et al* and Doleschall *et al* gives the desired title compound.

Examples 181-183

Following the procedure described in Example 180 but substituting in each case the appropriate β-diketone reagent for the 1-hydroxy-6-phenylhexane4,6-dione above, the following compounds may be prepared:

Ex. #	Name
181	2-Methylypropyl (5-trifluoromethyl-4-isoxazolyl) ketone;
182	1,1,2,2,3,3,3-Heptafluoropropyl (5-trifluoromethyl-4-isoxazolyl) ketone; and
183	3-Furanyl (5-trifluoromethyl-4-isoxazolyl) ketone.

Examples 184-229

Following the procedures described in Example 73 but substituting in each case the appropriate isoxazole precursor for the resultant compound of Example 1, the following compounds may be prepared:

Ex. #	Name
184	(3-Furanyl)methyl 2-cyano-3-hydroxycrotonate;
185	2-(1-Piperidyl)ethyl 2-cyano-3-hydroxycrotonate;
186	3-Pyridyl 2-cyano-3-hydroxycrotonate;
187	4-(2-methyl-5-(*p* -nitrophenyl)oxazolyl)methyl 2-cyano-3-hydroxycrotonate;
188	7-Chloro-4-quinolyl 2-cyano-3-hydroxycrotonate;
189	2-(4-Nitrophenyl)ethyl 2-cyano-3-hydroxycrotonate;
190	2-(4-Nitrophenyl)ethyl 4,4,4-trifluoro-2-cyano-3-hydroxycrotonate;
191	N-Benzyl-2-cyano-3-hydroxycrotonyl hydroxamide
192	N-(7-Trifluoromethyl-1,2,3,4-tetrahydroquinolinyl)-2-cyano-3-hydroxycrotonamide;
193	N-Cycloleucyl-2-cyano-3-hydroxycrotonamide;

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194 N-(L-Tyrosinyl methyl ester)-2-cyano-3-hydroxycrotonamide;
195 N-(1-Homopiperidinyl)-2-cyano-3-hydroxycrotonylhydrazide;
196 N-[2-(2-Carboxy)norbornyl]-2-cyano-3-hydroxycrotonamide;
197 N-(2-Thienylmethyl)-2-cyano-3-hydroxycrotonamide;
198 N-(2,6-Dimethylmorpholinyl)-2-cyano-3-hydroxycrotonamide;
199 N,N-Dimethylaminoethyl-2-cyano-3-hydroxycrotonamide;
200 N-[2-(1-Cyclohexenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
201 N-Benzyl-N-(2-norbornyl)-2-cyano-3-hydroxycrotonamide;
202 N-Convolvinyl-2-cyano-3-hydroxycrotonamide;
203 N-(4-Propylpiperidinyl)-2-cyano-3-hydroxycrotonamide;
204 N-{4-[(4-hydroxy-3-*t*-butyl)-phenoxyethoxy]phenyl}-2-cyano-3-hydroxycrotonamide;
205 N-4-[2-(Phenylaminocarbonyl)propionyl]phenyl-2-cyano-3-hydroxycrotonamide;
206 N-(2-Methyl-1-amyl)-2-cyano-3-hydroxy-4,4,4-trifluorocrotonamide;
207 N-(5-Morpholinylamyl)-2-cyano-3-hydroxycrotonamide;
208 N-(5-Diisopropylamino-1,3,4-thiadiazole-2-yl)-2-cyano-3-hydroxycrotonamide;
209 N-(L-Prolyl *t*-butyl ester)-2-cyano-3-hydroxycrotonamide;
210 N-(L-Leucyl-*t*-butyl ester)-2-cyano-3-hydroxycrotonamide;
211 N-(1-Cyanocyclopentylmethyl)-2-cyano-3-hydroxycrotonamide;
212 N-[(1-Carboxy)cycloheptyl]-N-ethyl-2-cyano-3-hydroxycrotonamide;
213 N-{4-[2-(2-Methoxyethoxy)ethoxy]phenyl}-2-cyano-3-hydroxycrotonamide;
214 N-(Glycine trityl ester)-2-cyano-3-hydroxycrotonamide;
215 N-{[2-(2-Chlorophenyl)]-1-oxocyclohexan-2-yl hydrochloride}-2-cyano-3-hydroxycrotonamide;
216 N-(5-*exo*-Norbornen-2-yl)-N-methyl-2-cyano-3-hydroxycrotonamide;
217 N-(β-Alanyl *t*-butyl ester)-2-cyano-3-hydroxycrotonamide;
218 N-Pyrrolidinyl-2-cyano-3-hydroxy-4,4,4-trifluorocrotonic acid hydrazide;
219 N-Morpholinyl-2-cyano-3-hydroxy-4,4,4-trifluorocrotonic acid hydrazide;
220 N-4-(3-Nitrophenyl)thiazol-2-yl 3-(2-methoxyphenyl)-3-hydroxy-2-cyanoacrylamide.
221 N-(3-Methylbutyl)-4,4,4-trifluoro-2-cyano-3-hydroxycrotonamide;
222 1-(3-Phenyl-2-cyano-3-hydroxyacryloylamino)-4-(4-toluenesulfonylamino)benzene;
223 N-Butyl-3-phenyl-2-cyano-3-hydroxyacrylamide;

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224 3-Hydroxypropyl (3-phenyl-2-cyano-3-hydroxyacryloyl) ketone;
225 2-Methylypropyl (4,4,4-trifluoro-2-cyano-3-hydroxycrotonyl) ketone;
226 2-Methoxyethyl-3-(4-nitrophenyl)-2-cyano-3-hydroxyacrylate;
227 1,1,2,2,3,3,3-Heptafluoropropyl (4,4,4-trifluoro-2-cyano-3-hydroxycrotonyl)ketone;
228 3-Furanylmethyl (4,4,4-trifluoro-2-cyano-3-hydroxycrotonyl) ketone; and
229 2-Furanylmethyl (4,4,4-trifluoro-2-cyano-3-hydroxycrotonyl) ketone.

Example 230

N-(4-Trifluoromethylphenyl)-5-(2-methoxyethyl)isoxazole-4-carboxamide

Step A: 4-(2-Methoxyethyl) isoxazole-4-carboxylic acid

Homologation of the α-methylene group of ethyl 5-methoxy-3-oxo-pentanoate with triethylorthoformate followed by cyclization with hydroxylamine hydrochloride as depicted in scheme I and described in Schenone *et al* and Doleschall *et al* gives the desired ethyl ester. Hydrolysis under the acidic conditions detailed in the cited references delivers the corresponding carboxylic acid.

Step B: 4-(2-Methoxyethyl) isoxazole-4-carboxylic acid chloride

The compound resulting from Step A and $SOCl_2$ are combined and stirred at reflux for 3 hours. The excess $SOCl_2$ is removed by distillation at atmospheric pressure. The residual acid chloride is purified via bulb-to-bulb distillation at high vacuum thereby affording the title compound.

Step C: N-(4-Trifluoromethylphenyl)-5-(2-methoxyethyl)isoxazole-4-carboxamide

To a solution of the compound resulting from Step B dry acetonitrile stirred at ambient temperature is added 2 equivalents of 4-trifluoromethylphenethyl amine in acetonitrile dropwise. After stirring for 75 minutes, the reaction is filtered and the collected precipitate is washed with acetonitrile (2x50 mL). The combined filtrates are concentrated *in vacuo* and the residual crude amide is purified by recrystallization from toluene and overnight vacuum drying.

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Example 231

2-(4-Trifluoromethylphenyl)ethyl 5-(2-methoxyethyl) isoxazole-4-carboxylate

To a solution of the compound resulting from Example 232 Step B in 12 mL of dry acetonitrile stirred at ambient temperature, is added 2 equivalents of 4-trifluoromethylphenethyl alcohol and 1.1 equivalents of pyridine in acetonitrile portionwise. The reaction is stirred for 8 hours and then 2 N HCl is added. The resulting mixture is extracted with EtOAc and the combined organic extracts are washed with water and brine, dried over $MgSO_4$, and filtered. The solvent is removed *in vacuo* to afford crude product which is purified by flash chromatography on silica gel eluting with an EtOAc-heptane gradient to afford the desired ester.

Examples 232-258

Following the procedures described in Example 230 but substituting in each case the appropriate amine reagent for the 4-trifluoromethylphenethyl amine of Step C, the following amide derivatives may be prepared:

Ex. #	Name
232	N-(4-Trifluoromethylphenyl)-5-(2-fluorophenyl)isoxazole-4-carboxamide;
233	N-(4-Fluorophenyl)-5-(4-fluorophenyl)isoxazole-4-carboxamide;
234	N-(4-Trifluoromethylphenyl)-5-(carbomethoxymethyl)isoxazole-4-carboxamide;
235	N-(4-Trifluoromethylphenyl)-5-(2-carbomethoxyethyl)isoxazole-4-carboxamide;
236	N-(2-Pyridyl)-5-(2-benzylphenyl)isoxazole-4-carboxamide;
237	N-(4-Trifluoromethylphenyl)-5-(3-carboethoxypropyl)isoxazole-4-carboxamide;
238	N-(4-*t*-Butylphenyl)-5-(methoxymethyl)isoxazole-4-carboxamide;
239	N-(4-Trifluoromethylphenyl)-5-(2-furanyl)isoxazole-4-carboxamide;
240	N-(2-Bromophenyl)-5-(4-hexadecyloxyphenyl)isoxazole-4-carboxamide;
241	N-(4-Trifluoromethylphenyl)-5-(2,4-bis(1,1,2-trifluoro-2-chloroethoxy)phenyl) isoxazole-4-carboxamide;
242	N-(2-Bromophenyl)-5-(5,6,7,8-tetrahydro-2-naphthyl)isoxazole-4-carboxamide;
243	N-(2,5-Dimethoxyphenyl)-5-(2-thienyl)isoxazole-4-carboxamide;

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244 N-(4-Trifluoromethylphenyl)-5-(3-N,N dimethylsulfonamidophenyl)isoxazole-4-carboxamide;

245 N-(4-Fluorophenyl)-5-(*E* -2-phenylethylenyl)isoxazole-4-carboxamide;

246 N-(4-Trifluoromethylphenyl)-5-(2-methylsulfonylphenyl)isoxazole-4-carboxamide;

247 N-Morpholino-5-(4-phenoxyphenyl)isoxazole-4-carboxamide;

248 N-(4-Trifluoromethylphenyl)-5-((2-phenoxyethoxy)phenyl)isoxazole-4-carboxamide;

249 N-(4-Trifluoromethylphenyl)-5-(4-*t*-butylphenyl)isoxazole-4-carboxamide;

250 N-(4-Trifluoromethylphenyl)-5-(3-nitro-4-(2-(4-(2-(2,4,4,Trimethylpentyl) phenoxy) ethoxy)phenyl)isoxazole-4-carboxamide;

251 N-(4-Trifluoromethylphenyl)-5-(2-carbomethoxyphenyl)isoxazole-4-carboxamide;

252 N-(4-Trifluoromethylphenyl)-5-(2-methoxyethyl)isoxazole-4-carboxamide;

253 N-(2-(5-(4-t-Butylphenyl)thienyl))-5-(3-butenyl)isoxazole-4-carboxamide;

254 N-(4-(4-Trifluoromethylphenyl)phenyl)-5-(4-cyanophenyl)isoxazole-4-carboxamide;

255 N-(4-Trifluoromethylphenyl)-5-(6-undecyl)isoxazole-4-carboxamide

256 N-(4-Trifluoromethylphenyl)-5-(3,5-bis(trifluoromethyl)phenyl)isoxazole-4-carboxamide;

257 N-(4-Trifluoromethylphenyl)-5-(1-adamantyl)isoxazole-4-carboxamide; and

258 N-(4-Trifluoromethylphenyl)-5-(*E* -3-pentenyl)isoxazole-4-carboxamide.

Examples 259-260

Following the procedures described in Example 232 but substituting in each case the appropriate alcohol reagent for 4-trifluoromethylphenethyl alcohol, the following ester derivatives may be prepared:

Ex. #	Name
259	4-Trifluoromethylphenyl 5-((phenylsulfonyl)methyl)isoxazole-4-carboxylate; and
260	α–Naphthyl 5-((thiophenyl)methyl)isoxazole-4-carboxylate.

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Example 261

2-Methylypropyl (5-(2-pyridyl)-4-isoxazolyl) ketone

Homologation of the α-methylene group of 1-(2-pyridyl)-5-methyl-1,3-hexanedione with triethylorthoformate followed by cyclization with hydroxylamine hydrochloride as depicted in scheme II and described in Schenone *et al* and Doleschall *et al* gives the desired title compound.

Examples 262-263

Following the procedure described in Example 261 but substituting in each case the appropriate β-diketone reagent for the 1-(2-pyridyl)-5-methyl-1,3-hexanedione above, the following compounds may be prepared:

Ex. #	Name
262	3-Furanyl (5-(2-propenyl)-4-isoxazolyl) ketone; and
263	1,1,2,2,3,3,3-Heptafluoropropyl (5-cyclohexyl-4-isoxazolyl) ketone.

Example 264

N-[2-(4-Trifluoromethylphenyl)ethyl]-2-cyano-3-hydroxycrotonamide

To the compound resulting from Example 230 in MeOH stirred at 25 °C is slowly added 2 N NaOH solution . The reaction is then stirred at reflux for 3 hours followed by cooling to ambient temperature. Dilution with 50 mL of water followed by acidification with concentrated HCl affords a precipitate. The collected solid is washed with water and recrystalized twice from EtOH to give the title compound.

Examples 265-294

Following the procedures described in Example 266 but substituting in each case the appropriate isoxazole precursor for the resultant compound of Example 232, the following compounds may be prepared:

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Ex. #	Name
265	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2-fluorophenyl) acrylamide;
266	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4-fluorophenyl) acrylamide;
267	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-carbomethoxy crotonamide;
268	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-5-carbomethoxy-2-pentenamide;
269	N-(2-Pyridyl)-2-cyano-3-hydroxy-3-(2-benzylphenyl) acrylamide;
270	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-6-carboethoxy-2-hexenamide;
271	N-(4-*t*-Butylphenyl)-2-cyano-3-hydroxy-4-methoxy-crotonamide;
272	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4-hexadecyloxyphenyl) acrylamide;
273	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2,4-bis(1,1,2-trifluoro-2-chloroethoxy)phenyl) acrylamide;
274	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(5,6,7,8-tetrahydro-2-naphthyl) acrylamide;
275	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2-thienyl) acrylamide;
276	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(3-N,N dimethylsulfonamido phenyl) acrylamide;
277	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2-methylsulfonylphenyl) acrylamide;
278	N-Morpholino-2-cyano-3-hydroxy-3-(4-phenoxyphenyl) acrylamide;
279	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-((2-phenoxyethoxy)phenyl) acrylamide;
280	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(3-nitro-4-(2-(4-(2-(2,4,4,Trimethylpentyl) phenoxy) ethoxy)phenyl) acrylamide;
281	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2-carbomethoxyphenyl) acrylamide;
282	N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-5-methoxy-2-pentenamide;
283	N-(2-(5-(4-t-Butylphenyl)thienyl))-2-cyano-3-hydroxy-2,6-heptadienamide;
284	N-(4-(4-Trifluoromethylphenyl)phenyl)-2-cyano-3-hydroxy-3-(4-cyanophenyl) acrylamide;

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285 N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-(*n*-pentyl)non-2-enamide;

286 N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(3,5-bis(trifluoromethyl) phenyl) acrylamide;

287 N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(1-adamantyl) acrylamide;

288 N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-2,6-octadienamide;

289 4-Trifluoromethylphenyl-2-cyano-3-hydroxy-4-phenylsulfonyl crotonate;

290 α-Naphthyl 2-cyano-3-hydroxy-4-thiophenyl crotonate;

291 2-(4-Trifluoromethylphenyl)ethyl 2-cyano-3-hydroxy-5-methoxy-2-pentenoate;

292 3-Furanyl (1-cyano-2-hydroxy-2,4 pentadienyl) ketone;

293 2-Methylypropyl (1-cyano-2-hydroxy-2-(2-pyridyl)ethylenyl) ketone;

294 1,1,2,2,3,3,3-Heptafluoropropyl (1-cyano-2-hydroxy-2-cyclohexylethylenyl) ketone.

Example 295

In vitro Assay of Biological Activity

The *in vivo* immunosuppressant activity of the compounds of the present invention was determined using the human mixed lymphocyte reaction (HMLR) assay described by Kino, T. *et al.* in *Transplantation Proceedings*, XIX(5):36-39, Suppl. 6 (1987).

The *in vitro* immunosuppressant activity of the compounds of the present invention was also determined in a one way allogeneic mixed leukocyte response (MLR) assay using rat lymph node and spleen cells, conducted as follows: Responder cells were obtained from the lymph nodes of Brown Norway rats (Harlan Sprague Dawley, Inc., Indianapolis, IN) and the stimulator cells were isolated from the spleens of Lewis rats (Harlan Sprague Dawley, Inc., Indianapolis, IN). 200-250 gram rats were sacrificed by asphyxiation with CO_2 and the popliteal and mesenteric lymph nodes or spleen were removed by sterile dissection. The tissue was placed in RPMI 1640 supplemented with 10 % heat-inactivated fetal bovine serum, 2 mM L-glutamine, 50 μM 2-mercaptoethanol, 50 units/mL penicillin G, and 50 μg/mL streptomycin (complete RPMI medium). After mechanically disrupting the tissue and allowing debris to settle at 1 x g, the suspended cells were aspirated. The cell suspensions were centrifuged 10 min at 400 x g and the responder cells resuspended in complete RPMI medium at 2 X 10^6 cells/mL. To remove red cells, the spleen cells were suspended in 0.14 M NH_4Cl/0.017 M Tris-HCl lysing buffer, pH 7.4, for 2 minutes, mixed

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with RPMI 1640, and centrifuged as before. The spleen cells were subsequently washed three times by centrifugation in RPMI 1640. To inhibit their ability to proliferate, spleen cells were suspended at 1 x 10^7 cells/mL in complete RPMI medium and incubated in the presence of 25 µg/mL of mitomycin C for 30 minutes at 37 °C. The mitomycin C-treated spleen cells were washed three times by centrifugation in RPMI 1640 before being suspended in complete RPMI medium at 4 x 10^6 cells/mL.

For the MLR, 1 x 10^5 lymph node cells were mixed with 5 x 10^5 mitomycin C-treated spleen cells in 0.2 mL of complete RPMI 1640 and cultured in 95% air / 5% CO_2 atmosphere for 120 hours at 37 °C. Test compounds were dissolved at 10 mM in dimethylsulfoxide, diluted in complete RPMI medium, and 25 µL of the test compound was added to the lymph node cells before addition of the spleen cells. During the final 6 hours, the cells were labeled with 0.5 µCi per well of tritiated thymidine (^{3}H-TdR; DuPont NEN Research Products, Boston, MA). The cells were harvested by vacuum filtration onto glass fiber filters and the filter radioactivity measured with a MATRIX 9600 direct beta counter (Packard Instrument Company, Meriden, CT).

The results of the *in vitro* and *in vivo* assays, shown below in Table 1, demonstrate that the compounds tested are effective immunomodulators at micromolar concentrations.

Table 1

Example	Human MLR % Inhibition at 10 µM*	Rat MLR % Inhibition at 10 µM*
1	< 10	50
2	< 10	< 10
3	< 10	< 10
4	13	25
5	18(0.1)	< 10
6	25(0.1)	< 10
7	17	< 10
8	< 10	80
9	< 10	26
10	68	<10
11	42	-
12	43	-
13	< 10	< 10
14	< 10	< 10
15	38	13 (0.1)

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16	42	29
17	55	50
18	32	< 10
19	19	12
20	20	15
21	24	34
22	48	46(0.1)
23	45	29
24	44	< 10
25	25	< 10
26	44	38(0.1)
27	26	23
28	36	24
29	36	21
30	36	44
31	50	25
32	17	12
33	27	23
34	27	< 10
35	< 10	< 10
36	31	25
37	< 10	39
38	< 10	20
39	36	27
40	37	< 10
41	50	15
42	39	< 10
43	27	16
44	46	38
45	34	< 10
46	94	99
47	22	42(0.1)
48	30	25
49	75	13
50	54	16
51	40	98

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52	< 10	35
53	45	52(0.1)
54	< 10	32
55	40	< 10
56	39	48
57	55	26
58	35	< 10
59	38	< 10
60	34	< 10
61	49	19
62	48	< 10
63	46	100
64	33	< 10
65	28(0.01)	< 10
66	46	13 (0.1)
67	29	43
68	40	< 10
69	19	< 10
70	25	43(0.1)
71	25	19
72	43	73
73	21	79
74	< 10	< 10
75	< 10	75
76	22	< 10
77	34	< 10
78	25(1.0)	38
79	< 10	< 10
80	21	< 10
81	64	< 10
82	33	-
83	< 10	< 10
84	< 10	< 10
85	44	27
86	35	27
87	46	49(0.1)

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88	< 10	< 10
89	34	-
90	26	< 10
91	53	< 10
92	34	32
93	55	20
94	32	33(1.0)
95	29	< 10
96	30	24
97	31	< 10
98	40	61(0.1)
99	18	< 10
100	36	< 10
101	36	< 10
102	19	< 10
103	< 10	38
104	52	< 10
105	< 10	< 10
106	44	< 10
107	26	27(1.0)
108	25	< 10
109	25	38(1.0)
110	32	< 10
111	63	< 10
112	53	35
113	30	< 10
114	36	< 10
115	74	100
116	53	39(1.0)
117	48	32
118	< 10	< 10
119	31	< 10
120	35	65
121	31	18
122	< 10	< 10
123	39	< 10

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124	< 10	< 10
125	< 10	22
126	18	< 10
127	30	64
128	31	35(1.0)
129	45	45
130	38	33(0.1)
131	42	< 10
132	50	< 10
133	45	< 10
134	32	36(1.0)
135	46	97
136	< 10	75
137	29	23(1.0)
138	57	17
139	30	21(1.0)

* Concentration at 10 μM unless otherwise indicated in parentheses

It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, formulations and/or methods of use of the invention, may be made without departing from the spirit and scope thereof.

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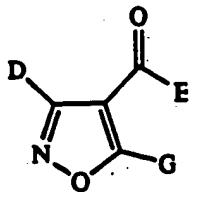
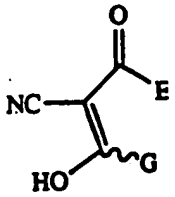
What is claimed is:

1. A compound having a formula selected from the group consisting of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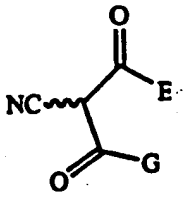

and the respective pharmaceutically acceptable salts, esters and prodrugs thereof, wherein

E is selected from the group consisting of $-R^{14}$, [redacted], $-SR^{14}$, $-OR^{14}$, and $-CR^{14}R^{15}R^{16}$, where R^{14}, R^{15} and R^{16} are independently selected from the group consisting of

(I) [redacted]

(II) $-NR^6R^7$, where R^6 and R^7 are independently selected from the group consisting of

(a) hydrogen,
(b) alkyl,
(c) alkenyl,
(d) acyl,
(e) aryl,
(f) heterocyclic,
(g) biaryl,
(h) cycloalkyl,
(i) arylalkyl,
(j) hydroxyalkyl, and
(k) arylsulfonyl,

and each radical R^6 and R^7, when other than hydrogen, is optionally substituted with between one and three substituents independently selected from the group consisting of

(i) halogen,
(ii) haloalkyl,
(iii) haloalkoxy,
(iv) -CHO,

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(v) -CN,
(vi) -C(O)OH,
(vii) -C(O)O-(C_1-to-C_6 alkyl),
(viii) -N_3,
(ix) -NO_2,
(x) -OH, and
(xi) oxo;

(III) -(C_1-to-C_{10} alkyl), where alkyl comprises straight and branched alkyl, cycloalkyl, (cycloalkyl)alkyl, bicycloalkyl and (bicycloalkyl)alkyl, optionally substituted with between one and six substituents independently selected at each instance from the group consisting of

(a) R^{10}, where R^{10} is selected at each instance from the group consisting of

(i) halogen,
(ii) haloalkyl,
(iii) haloalkoxy,
(iv) -OH,
(v) -$(CH)_mNR^6R^7$, where m is zero to six,
(vi) -CHO,
(vii) -$(CH_2)_mOR^6$,
(viii) -$CH(OR^{12'})(OR^{12''})$, where $R^{12'}$ and $R^{12''}$ are independently -(C_1-to-C_3 alkyl) or, taken together, form an ethylene or propylene bridge,
(ix) -$(CH_2)_m$-$OC(O)R^6$,
(x) -CN,
(xi) -C(O)OH,
(xii) -C(O)O-(C_1-to-C_6 alkyl),
(xiii) -$C(O)NR^6R^7$,
(xiv) -(C_3-to-C_7 cycloalkyl),
(xv) aryl substituted with X, Y and Z,
(xvi) -NO_2,
(xvii) -N_3,
(xviii) guanidino, optionally substituted with a substituent selected from the group consisting of loweralkyl, aryl, acyl, arylsulfonyl, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl and alkylsulfonyl,

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(xix) $-OR^{11}$, where R^{11} is selected at each instance from the group consisting f

(a') $-P(O)(OH)O^-M^+$, where M^+ is a positively charged inorganic or organic counterion,

(b') $-S(O)_2O^-M^+$, and

(c') $-CO(CH_2)_mC(O)O^-M^+$,

(xx) oxo,

(xxi) epoxy,

(xxii) thiooxo,

(xxiii) -SH,

(xxiv) $-S(O)_sR^6$, where s is zero, one or two, and

(xxv) $-S(O)_tNR^6R^7$, where t is one or two,

where X, Y, and Z are each independently selected at each instance from the group consisting of

(a') hydrogen,

(b') halogen,

(c') haloalkyl,

(d') $-(C_1\text{-to-}C_7$ alkyl),

(e') $-(C_2\text{-to-}C_6$ alkenyl),

(f') $-(C_2\text{-to-}C_6$ alkynyl),

(g') $-(CH_2)_mNR^6R^7$,

(h') -CN,

(i') -CHO,

(j') $-(CH_2)_mOR^6$,

(k') $-(CH_2)_mC(O)OR^6$,

(l') $-(CH_2)_mOC(O)R^6$,

(m') $-CH(OR^{12'})(OR^{12''})$,

(n') $-C(O)NR^6R^7$,

(o') $-NO_2$,

(p') $-N_3$,

(q') guanidino optionally substituted with a substituent selected from the group consisting of lower alkyl, aryl, acyl, arylsulfonyl, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl and alkylsulfonyl,

(r') $-OR^{11}$

(s') $-S(O)_sR^6$, and

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(t') $-S(O)_tNR^6R^7$,

or any two adjacent of X, Y and Z, taken together with the carbon atoms to which they are attached, form a 5- to 7-membered ring which includes between zero and two additional heteroatoms independently selected from the group consisting of -O-, $-S(O)_s-$ and $-N(R^8)-$,

(b) $R^{10'}$, where $R^{10'}$ is selected at each instance from the group consisting of

(i) $-(CH_2)_mNR^{6'}R^{7'}$,
(ii) $-(CH_2)_mOR^{6'}$,
(iii) $-(CH_2)_mOC(O)R^{6'}$,
(iv) $-C(O)NR^{6'}R^{7'}$,
(v) $-S(O)_tNR^{6'}R^{7'}$,
(vi) $-S(O)_sR^{6'}$,
(vii) aryl substituted with X', Y' and Z', where X', Y' and Z' are independently selected at each instance from the group consisting of
(a') X, Y and Z,
(b') $-(CH_2)_mNR^{6'}R^{7'}$,
(c') $-(CH_2)_mOR^{6'}$,
(d') $-(CH_2)_mC(O)OR^{6'}$,
(e') $-(CH_2)_mOC(O)R^{6'}$,
(f') $-C(O)NR^{6'}R^{7'}$,
(g') $-S(O)_tNR^{6'}R^{7'}$, and
(h') $-S(O)_sR^{6'}$, and
(viii) heterocyclic substituted with X', Y' and Z'

where $R^{6'}$ and $R^{7'}$ are independently selected at each instance from the group consisting of

(i) hydrogen,
(ii) -(C_1-to-C_{10} alkyl) optionally substituted with between one and six substituents selected from the group consisting of
(a') R^{10},
(b') biaryl substituted with X, Y and Z,
(c') -Q-aryl where aryl is substituted with X, Y and Z,
(d') -Q-heterocyclic where heterocyclic is substituted with X, Y and Z,

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(e') -Q-biaryl, where biaryl is substituted with X, Y and Z,

(f') -aryl-Q-aryl', where aryl and aryl' are each independently substituted with X, Y and Z,

(g') -heterocyclic-Q-heterocyclic', where heterocyclic and heterocyclic' are each independently substituted with X, Y and Z,

(h') -heterocyclic-Q-aryl, where heterocyclic and aryl are each independently substituted with X, Y and Z,

(i') -aryl-Q-heterocyclic, where heterocyclic and aryl are each independently substituted with X, Y and Z, and

(j') $-NR^8R^{8'}$, where R^8 and $R^{8'}$ are independently selected at each instance from the group consisting of

(i') hydrogen,

(ii') $-R^{10}$ other than halogen, $-NO_2$ and $-N_3$,

(iii') -(C_1-to-C_6 alkyl) optionally substituted with between one and three substituents R^{55} where each R^{55} is independently selected from the group consisting of amino, aryl, guanidino, heterocyclic, monoalkylamino, dialkylamino, acylamino, alkoxycarbonylamino, arylalkyloxycarbonylamino, aryloxycarbonylamino, acylguanidino, arylsulfonylguanidino, alkoxycarbonylguanidino, arylalkyloxycarbonylguanidino, aryloxycarbonylguanidino, alkoxycarbonyl, alkylsulfonyl, arylsulfonyl, N-alkylcarboxamido, N,N-dialkylcarboxamido, N-arylcarboxamido and N,N-diarylcarboxamido,

(iv') -(C_2-to-C_6 alkenyl) optionally substituted with between one and three substituents R^{55}, and

(v') -(C_3-to-C_6 alkynyl) optionally substituted with between one and three substituents R^{55},

or where R^8 and $R^{8'}$ and the nitrogen atom to which they are attached form an optionally substituted 3- to 7-membered heterocyclic ring which includes between zero and two additional heteroatoms independently selected from the group consisting of -O-, $-S(O)_s-$ where s is zero, one or two, and $-NR^8-$,

(k') $-S(O)_sR^8$, and

(l') $-S(O)_tNR^8R^{8'}$,

(iii) aryl substituted with X, Y and Z, and

(iv) heterocyclic substituted with X, Y and Z,

or where R^6 and R^7 and the nitrogen atom to which they are attached form a 3- to 7-membered heterocyclic ring comprising between zero and two additional heteroatoms

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independently selected from the group consisting of -O-, -S(O)$_s$- and -NR^8-, in which each ring valency is substituted with a compatible radical selected from the group consisting of

(i) -R^{66}, and

(ii) -QR^{66}, where R^{66} is selected at each instance from the group consisting of

(a') hydrogen,

(b') R^{10},

(c') aryl substituted with X, Y and Z

(d') heterocyclic substituted with X, Y and Z,

(e') biaryl substituted with X, Y and Z,

(f') -aryl-Q-aryl', where aryl and aryl' are each independently substituted with X, Y and Z,

(g') -heterocyclic-Q-heterocyclic', where heterocyclic and heterocyclic' are each independently substituted with X, Y and Z,

(h') -heterocyclic-Q-aryl, where heterocyclic and aryl are each independently substituted with X, Y and Z,

(i') -aryl-Q-heterocyclic, where heterocyclic and aryl are each independently substituted with X, Y and Z,

(j') -NR^{8}R$^{8'}$,

(k') -S(O)$_s$R^8, and

(l') -S(O)$_t$NR^{8}R$^{8'}$,

and where Q is selected at each instance from the group consisting of

(i) -(C$_1$-to-C$_6$ alkylene)-,

(ii) -(C$_2$-to-C$_6$ alkenylene)-,

(iii) -(C$_2$-to-C$_6$ alkynylene)-,

(iv) -(CH$_2$)$_m$O-, where m is zero to six,

(v) -O(CH$_2$)$_m$-, where m is zero to six,

(vi) -N(R^8)C(O)-,

(vii) -C(O)N(R^8)-,

(viii) -S(O)$_s$-, where s is zero, one or two,

(ix) -N(R^8)-,

(x) -N(R^8)S(O)$_t$-,

(xi) -S(O)$_t$N(R^8)-,

(xii) -C(O)-,

(xiii) -N=N- and

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(xiv) -C(S)-,

(c) heterocyclic substituted with X, Y and Z,
(d) biaryl substituted with X, Y and Z,
(e) -Q-aryl,
(f) -Q-heterocyclic where heterocyclic is substituted with X, Y and Z,
(g) -Q-biaryl, where biaryl is substituted with X, Y and Z,
(h) -aryl-Q-aryl', where aryl and aryl' are each independently substituted with X, Y and Z,
(i) -heterocyclic-Q-heterocyclic', where heterocyclic and heterocyclic' are each independently substituted with X, Y and Z,
(j) -heterocyclic-Q-aryl, where heterocyclic and aryl are each independently substituted with X, Y and Z, and
(k) -aryl-Q-heterocyclic, where heterocyclic and aryl are each independently substituted with X, Y and Z;

(IV) -(C_2-to-C_{10} alkenyl), where alkenyl comprises branched, unbranched, cyclic and bicyclic alkenyl, optionally substituted with between one and six substituents independently selected at each instance from the group consisting of
(a) R^{10},
(b) $R^{10'}$,
(c) heterocyclic substituted with X, Y and Z,
(d) biaryl substituted with X, Y and Z,
(e) -Q-aryl, where aryl is substituted with X, Y and Z,
(f) -Q-heterocyclic, where heterocyclic is substituted with X, Y and Z,
(g) -Q-biaryl, where biaryl is substituted with X, Y and Z,
(h) -aryl-Q-aryl', where aryl and aryl' are each independently substituted with X, Y and Z,
(i) -heterocyclic-Q-heterocyclic', where heterocyclic and heterocyclic' are each independently substituted with X, Y and Z,
(j) -heterocyclic-Q-aryl, where heterocyclic and aryl are each independently substituted with X, Y and Z, and
(k) -aryl-Q-heterocyclic, where heterocyclic and aryl are each independently substituted with X, Y and Z;

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(V) -(C_3-to-C_{10} alkynyl), where alkynyl comprises branched and cyclic alkynyl, optionally substituted with between one and six substituents independently selected at each instance from the group consisting of

(a) R^{10},

(b) $R^{10'}$,

(c) heterocyclic substituted with X, Y and Z,

(d) biaryl substituted with X, Y and Z,

(e) -Q-aryl, where aryl is substituted with X, Y and Z,

(f) -Q-heterocyclic, where heterocyclic is substituted with X, Y and Z,

(g) -Q-biaryl, where biaryl is substituted with X, Y and Z,

(h) -aryl-Q-aryl', where aryl and aryl' are each independently substituted with X, Y and Z,

(i) -heterocyclic-Q-heterocyclic', where heterocyclic and heterocyclic' are each independently substituted with X, Y and Z,

(j) -heterocyclic-Q-aryl, where heterocyclic and aryl are each independently substituted with X, Y and Z, and

(k) -aryl-Q-heterocyclic, where heterocyclic and aryl are each independently substituted with X, Y and Z;

(VI) aryl substituted with X', Y' and Z'.

(VII) heterocyclic substituted with X', Y' and Z';

(VIII) biaryl substituted with X', Y' and Z';

(IX) -aryl-heterocyclic, where heterocyclic and aryl are each independently substituted with X', Y' and Z';

(X) -heterocyclic-aryl, where heterocyclic and aryl are each independently substituted with X', Y' and Z';

(X) -Q-aryl where aryl is substituted with X', Y' and Z';

(XI) -Q-heterocyclic where heterocyclic is substituted with X', Y' and Z';

(XII) -Q-biaryl, where biaryl is substituted with X', Y' and Z';

(XIII) -aryl-Q-aryl', where aryl and aryl' are each independently substituted with X', Y' and Z';

(XIV) -heterocyclic-Q-heterocyclic', where heterocyclic and heterocyclic' are each independently substituted with X', Y' and Z';

(XV) -heterocyclic-Q-aryl, where heterocyclic and aryl are each independently substituted with X', Y' and Z'; and

(XVI) -aryl-Q-heterocyclic, where heterocyclic and aryl are each independently substituted with X', Y' and Z';

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D is selected from the group consisting f

(I) hydrogen;

(II) loweralkyl;

(III) -C(O)R^9 where R^9 is selected from the group consisting of

(a) hydrogen,

(b) -OH,

(c) $-O^-M^+$,

(d) -(C_1-to-C_4 alkyl), where alkyl comprises branching alkyl,

(e) -(C_1-to-C_4 alkoxy), where alkoxy comprises branching alkoxy,

(f) -(C_1-to-C_4 hydroxyalkyl),

(g) -(C_1-to-C_4 thioalkyl),

(h) -$(CH_2)_{nn}$-(phenyl), where nn is between zero and four,

(i) -$(CH_2)_n$-NR^4R^5,

(j) -$(CH_2)_m$-(morpholino),

(k) -NR^4R^5,

(l) -C(O)NR^4R^5, where R^4 and R^5 are independently selected from the group consisting of

(i) -hydrogen,

(ii) -(C_1-C_6 alkyl) optionally substituted with halogen, and

(iii) phenyl substituted with X, Y and Z,

(m) -C(O)OR^4,

(n) phenyl substituted with X, Y and Z,

(o) -O-phenyl, where phenyl is substituted with X, Y and Z,

(p) -O-$(CH_2)_m$-(morpholino), and

(q) -S-$(CH_2)_{nn}$-(phenyl);

(IV) phenyl;

(V) 2-chlorophenyl;

(VI) 2,4-dichlorophenyl; and

(VII) 2-chloro-4-fluorophenyl; and

G is selected from the group consisting of

(I) -$NR^{24}R^{25}$, where R^{24} and R^{25} and the nitrogen atom to which they are attached form a 3- to 7-membered heterocyclic ring comprising between zero and two additional heteroatoms independently selected from the group consisting of -O-, -$S(O)_s$- and

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-NR^8-, in which each ring valency is substituted with a compatible radical selected at each instance from the group consisting of

(a) -R^{66},

(b) -Q-R^{66},

(c) -R^{67}, and

(d) -Q-R^{67},

where R^{67} is selected at each instance from the group consisting of

(i) -$CH(OR^{12'})(OR^{12''})$, and

(ii) guanidino optionally substituted with a substituent selected from the group consisting of loweralkyl, aryl, acyl, arylsulfonyl, alkoxycarbonyl, arylalkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl;

(II) aryl substituted with X', Y' and Z';

(III) heterocyclic substituted with X', Y' and Z';

(IV) biaryl substituted with X', Y' and Z';

(V) -heterocyclic-aryl, where heterocyclic and aryl are each independently substituted with X', Y' and Z';

(VI) -aryl-heterocyclic, where heterocyclic and aryl are each independently substituted with X', Y' and Z';

(VII) -Q-aryl , where aryl is substituted with X', Y' and Z';

(VIII) -Q-heterocyclic, where heterocyclic is substituted with X', Y' and Z';

(IX) -Q-biaryl, where biaryl is substituted with X', Y' and Z';

(X) -aryl-Q-aryl', where aryl and aryl' are each independently substituted with X', Y' and Z';

(XI) -heterocyclic-Q-heterocyclic', where heterocyclic and heterocyclic' are each independently substituted with X', Y' and Z';

(XII) -heterocyclic-Q-aryl, where heterocyclic and aryl are each independently substituted with X', Y' and Z';

(XIII) -aryl-Q-heterocyclic, where heterocyclic and aryl are each independently substituted with X', Y' and Z';

(XIV) -R^{14};

(XV) -OR^{14};

(XVI) -$S(O)_sR^{14}$;

(XVII) -$CR^{14}R^{15}R^{16}$;

(XVIII) -$C{=}CR^{14}R^{15}$;

(XIX) -$C{\equiv}CR^{14}$;

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(XX) -C=NR^{14};
(XXI) -NR^{14}R^{15}; and
(XXII) Z,

subject to the provisos that

(I) when E is -NHCH$_2$-(heterocyclic), then G is other than pyrrolyl;

(II) when E is selected from the group consisting of
(a) -N(R^2)-[(C$_1$-to-C$_{10}$ alkylene)-C(O)O-(C$_1$-to-C$_4$ alkyl)], where R^2 is selected from the group consisting of
(i) hydrogen
(ii) -(C$_1$-to-C$_4$ alkyl),
(iii) phenyl, and
(iv) benzyl,
(b) -N(R^2)-(aryl),
(c) -N(R^2)-(heterocyclic),
(d) -N(R^2)-(heterocyclic)-(aryl),
(e) -N(R^2)-(biaryl),
(f) -N(R^2)-(phenyl)-O-(aryl),
(g) -N(R^2)-(phenyl)-C(O)-(aryl),
(h) -N(R^2)-C(CH$_3$)$_2$-CH$_2$-(aryl),
(i) -OH,
(j) -NH$_2$,
(k) -SH,
(l) methyl,
(m) hydrogen,
(n) N-morpholino,
(o) N-thiomorpholino, and
(p) N-piperidinyl optionally substituted with -(C$_1$-to-C$_2$ alkyl),
then G is other than R^{77} where R^{77} is a substituent selected from the group consisting of
(a) -(C$_1$-to-C$_6$ alkyl) optionally substituted with halogen,
(b) phenyl,
(c) benzyl, and
(d) -(C$_3$-to-C$_6$ cycloalkyl);

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(III) when E is selected from the group consisting of -S-phenyl and -O-phenyl where phenyl is substituted with X, Y and Z, then G is other than -(C_1-to-C_4 alkyl); and

(IV) when E is phenyl substituted with X, Y and Z, then G is other than a substituent selected from the group consisting of

(a) -(C_1-to-C_6 alkyl) optionally substituted with halogen,

(b) -(C_1-to-C_6 alkenyl) optionally substituted with halogen,

(c) -(C_5-to-C_6 cycloalkenyl),

(d) -(C_3-to-C_6 cycloalkyl),

(e) -(phenyl)-R^{76}, where R^{76} is a substituent selected from the group consisting of

(i) -C(O)R^{77},

(ii) -CN,

(iii) -NO_2,

(iv) -$NR^{78}R^{79}$, where R^{78} and R^{79} are independently selected from the group consisting of -(C_1-to-C_6 alkyl) radicals, and

(v) halogen,

(f) -(benzyl)-R^{76}, and

(g) -C(O)OR^{77}.

2. A compound according to Claim 1 wherein D is selected from the group consisting of hydrogen and -C(O)R^9.

3. A compound according to Claim 1 wherein G is selected from the group consisting of

(a) hydrogen,

(b) -(C_1-to-C_6 alkyl), including branching alkyl, optionally substituted with between one and six halogen substituents, and

(c) phenyl substituted with X, Y and Z.

4. A compound according to Claim 3 wherein G is methyl.

5. A compound according to Claim 1 wherein E is selected from the group consisting of -$NR^{14}R^{15}$, -OR^{14} and -$CR^{14}R^{15}R^{16}$.

6. A compound according to Claim 5 wherein E is -$NR^{14}R^{15}$.

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7. A compound according to Claim 6 wherein R^{14} is selected from the group consisting of

(a) aryl substituted with X', Y' and Z',

(b) heterocyclic substituted with X', Y' and Z',

(c) -aryl-heterocyclic, where aryl and heterocyclic are each independently substituted with X', Y' and Z', and

(d) -heterocyclic-aryl, where aryl and heterocyclic are each independently substituted with X', Y' and Z'.

8. A compound according to Claim 6 wherein R^{15} is selected from the group consisting of

(a) hydrogen,

(b) -(C_1-to-C_6 alkyl), where alkyl comprises branched alkyl, and

(c) -(C_1-to-C_6 alkyl) substituted with between one and six halogen substituents.

9. A compound according to Claim 2 wherein

E is selected from the group consisting of $-NR^{14}R^{15}$, $-OR^{14}$ and $-CR^{14}R^{15}R^{16}$;

D is hydrogen; and

G is selected from the group consisting of

(a) hydrogen,

(b) -(C_1-to-C_6 alkyl), including branching alkyl, optionally substituted with between one and six halogen substituents, and

(c) phenyl substituted with X, Y and Z.

10. A compound selected from the group consisting of

5-Methyl-isoxazole-4-carboxylic acid 2-(4-trifluoromethylphenyl)ethylamide;
5-Methyl-isoxazole-4-carboxylic acid 2-(4-fluorophenyl)ethylamide;
5-Methyl-isoxazole-4-carboxylic acid 2-phenylpropylamide;
5-Methyl-isoxazole-4-carboxylic acid 2-(4-nitrophenyl)ethylamide;
5-Methyl-isoxazole-4-hydroxamic acid benzylamide;
5-Methyl-isoxazole-4-carboxylic acid 4-fluorophenylhydrazide;
5-Methyl-isoxazole-4-carboxylic acid (7-trifluoromethyl-1,2,3,4-tetrahydroquinolinyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (6-methyl-1,2,3,4-tetrahydroquinolinyl)amide;
5-Methyl-isoxazole-4-carboxylic acid isobutylamide;

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5-Methyl-isoxazole-4-carboxylic acid (n-pentyl)amide;
5-Methyl-isoxazole-4-carboxylic acid pyrrolidinehydrazide;
5-Methyl-isoxazole-4-carboxylic acid morpholinohydrazide;
5-Methyl-isoxazole-4-carboxylic acid 4-trifluoromethylbenzimide;
5-Methyl-isoxazole-4-carboxylic acid 2-fluoroethylamide;
5-Methyl-isoxazole-4-carboxylic acid *trans*-4-(tert-butylcyclohexyl)amide;
5-Methyl-isoxazole-4-carboxylic acid *cis*-4-(tert-butylcyclohexyl)amide;
5-Methyl-isoxazole-4-carboxylic acid diethylamide;
5-Methyl-isoxazole-4-carboxylic acid ethylamide;
5-Methyl-isoxazole-4-carboxylic acid 2,2,2-trifluoroethylamide;
5-Methyl-isoxazole-4-carboxylic acid allylamide;
5-Methyl-isoxazole-4-carboxylic acid propargylamide;
5-Methyl-isoxazole-4-carboxylic acid (acetonitrile)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-methoxyethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (3-methoxypropyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-diethoxyacetal)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-thioethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-hydroxyethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-hydroxybutyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-piperidinoethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-methylpiperazino)amide;
5-Methyl-isoxazole-4-carboxylic acid (ethylglycinate)amide;
5-Methyl-isoxazole-4-carboxylic acid (3-propionic acid)amide;
5-Methylisoxazole-4-carboxylic acid (1-piperidino)amide;
5-Methylisoxazole-4-carboxylic acid (4-chlorophenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-methylcyclohexyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-norbornyl)amide;
5-Methyl-4-{4-(3-trifluoromethylphenyl)piperazine-1-ylcarbonyl}-isoxazole;
5-Methyl-isoxazole-4-carboxylic acid (cyclobutylmethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (norephedrine)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-methoxycarbonyl-cyclohexylmethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-hydroxyphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-{(4-phenyl)-benzyl}amide;
5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-(4-phenoxy)-benzylamide;
5-Methyl-isoxazole-4-carboxylic acid {2-[(2-chloro-4-t-butyl-phenoxy)methyl]benzyl}amide;
5-Methyl-isoxazole-4-carboxylic acid (furfuryl)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-triflu romethoxy-phenyl)hydrazide ;

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5-Methyl-isoxazole-4-carboxylic acid {(-)-*cis*-myrtanyl}amide;
5-Methyl-isoxazole-4-carboxylic acid (3-aminopropyl)amide;
5-Methylisoxazole-4-carboxylic acid (4-methoxyphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid {(4S)-benzyl-oxazolidinone}imide;
5-Methyl-isoxazole-4-carboxylic acid (4-methylphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid {(+)-norephedrine}amide;
5-Methyl-isoxazole-4-carboxylic acid (4-ethylphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid {2-hydroxy-5-(7-chloro-6-(ethoxycarbonylmethoxy)benzisoxazol-3-yl)benzyl}amide;
5-Methyl-isoxazole-4-carboxylic acid {4-(2,3-dichloro-4-(ethoxycarbonylmethoxy)benzoyl)benzyl}amide;
5-Methyl-isoxazole-4-carboxylic acid (aziridinyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (4-hydroxyphenethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (2-phenylethyl)amide;
5-Methyl-isoxazole-4-carboxylic acid cinnamimide;
5-Methyl-isoxazole-4-carboxylic acid 4-chlorocinnamimide;
5-Methyl-isoxazole-4-carboxylic acid {L-(S)-amphetamine}amide;
5-(3-Butenyl) isoxazole-4-carboxylic acid (4-trifluoromethylphenyl)amide;
5-Methyl-isoxazole-4-carboxylic acid cycloleucinolamide;
5-Methyl-isoxazole-4-carboxylic acid (tyrosine methyl ester)amide;
5-Methyl-isoxazole-4-carboxylic acid 1-aminohomopiperidinehydrazide;
5-Methyl-isoxazole-4-carboxylic acid (2-amino-2-norbornanecarboxylic acid)amide;
5-Methyl-isoxazole-4-carboxylic acid 2-thienylmethylamide;
5-Methyl-isoxazole-4-carboxylic acid (2,6-dimethylmorpholin-4-yl)amide;
5-Methyl-isoxazole-4-carboxylic acid 2-(N,N-dimethyl)aminoethylamide;
5-Methyl-isoxazole-4-carboxylic acid 2-cyclohex-1-enylethylamide;
5-Methyl-isoxazole-4-carboxylic acid 3-methoxypropylamide;
Ethyl 4-[3,5-di(5-methyl-isoxazole-4-carbonylamino)]-1H-1,2,4-triazolin-1-yl)benzoate]amide;
5-Methyl-isoxazole-4-carboxylic acid N-benzyl-N-norbornylamide;
5-Methyl-isoxazole-4-carboxylic acid (convolvinyl)amide;
5-Methyl-isoxazole-4-carboxylic acid 4-propylpiperidineamide;
5-Methyl-isoxazole-4-carboxylic acid {4-[(4-hydroxy-3-tert-butyl)-phenoxyethoxy]phenyl}amide;
5-Methyl-isoxazole-4-carboxylic acid 4-[2-(phenylaminocarbonyl)-propionyl]anilide;
5-Trifluoromethyl-isoxazole-4-carboxylic acid 3-methyl-1-butylamide;
5-Methyl-isoxazole-4-carboxylic acid 5-(N-morpholino)pentylamide;

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5-Methyl-isoxazole-4-carboxylic acid (5-diisopropylamino-1,3,4-thiadiazol-2-yl)amide;
5-Methyl-isoxazole-4-carboxylic acid (L-proline *t* -butyl ester)amide;
5-Methyl-isoxazole-4-carboxylic acid (L-leucine-*t* -butyl ester)amide;
5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-(1-cyano)cyclopentylamide;
5-Methyl-isoxazole-4-carboxylic acid N-ethyl-N-(1-carboxyl)cycloheptylamide;
5-Methyl-isoxazole-4-carboxylic acid 4-[2-(2-methoxyethoxy)ethoxy]anilide;
5-Methyl-isoxazole-4-carboxylic acid (glycine trityl ester)amide;
5-Methyl-isoxazole-4-carboxylic acid (ketamine hydrochloride)amide;
5-Methyl-isoxazole-4-carboxylic acid N-methyl-N-(5,6-dehydro-exo-2-norbornyl)amide;
5-Methyl-isoxazole-4-carboxylic acid (β-alanine *t* -butyl ester)amide;
4-Trifluoromethyl benzoyl 5-trifluoromethyl-isoxazole-4-carboximide;
3-(3-Methoxy)phenoxycarbonyl-5-methyl-isoxazole-4-carboxylic acid 3-methylbutylamide;
3-(N,N-Dimethylaminocarbonyl)-5-methyl-isoxazole-4-carboxylic acid
3-(4-methoxyphenyl)propylamide;
3-(2-Chloro-4-fluorophenacyl)-5-methyl-isoxazole-4-carboxylic acid cyclohexylamide;
N (5-Phenyl-4-isoxazoyl)-N'-(4-toluenesulfonyl) 1,4-phenylenediamide;
5-Phenyl-isoxazole-4-carboxylic acid butylamide;
5-Trifluoromethyl-isoxazole-4-carboxylic acid (3-methylbutyl)amide;
5-(2-Methoxyphenyl)-isoxazole-4-carboxylic acid 4-(3-nitrophenyl)thiazol-2-ylamide;
2-(4-Trifluoromethylphenyl)ethyl 5-methyl isoxazole-4-carboxylate;
2-(4-Nitrophenyl)ethyl 5-methyl-isoxazole-4-carboxylate;
2-(4-Fluorophenyl)ethyl 5-methyl-isoxazole-4-carboxylate;
4-Chlorophenethyl 5-methylisoxazole-4-carboxylate;
4-Trifluoromethylphenyl 5-methylisoxazole-4-carboxylate;
Cinnamyl 5-methylisoxazole-4-carboxylate;
2-(3-Trifluoromethylphenyl)ethyl 5-methylisoxazole-4-carboxylate;
3-Phenylbutyl 5-methylisoxazole-4-carboxylate;
(3-Furanyl)methyl 5-methyl-isoxazole-4-carboxylate;
2-(1-Piperidyl)ethyl 5-methyl-isoxazole-4-carboxylate;
3-Pyridyl 5-methyl-isoxazole-4-carboxylate;
4-[2-Methyl-5-(4-nitrophenyl)oxazolyl]methyl 5-methyl-isoxazole-4-carboxylate;
7-Chloro-4-quinolyl 5-methyl-isoxazole-4-carboxylate;
2-Methoxyethyl 5-(4-nitrophenyl)isoxazole-4-carboxylate;
2-(4-Nitrophenyl)ethyl 5-trifluoromethylisoxazole-4-carboxylate;
3-Hydroxypropyl (5-phenyl-4-isoxazolyl) ketone;
2-Methylypropyl (5-trifluoromethyl-4-isoxazolyl) ketone;
1,1,2,2,3,3,3-Heptafluoropropyl (5-triflu romethyl-4-isoxazolyl) ketone;

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3-Furanyl (5-trifluoromethyl-4-isoxazolyl) ketone;
N[2-(4-Trifluoromethylphenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-(2-Phenylpropyl)-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Fluorophenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Nitrophenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-methoxycrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-ethoxycrotonamide;
N-[2-(4-Fluorophenyl)ethyl]-2-cyano-3-hydroxycrotonate;
N-[2-(4-Trifluoromethylphenyl)ethyl-2-cyano-3-hydroxycrotonate;
N-[n-Pentyl]-2-cyano-3-hydroxycrotonamide;
N-(Isobutyl)-2-cyano-3-hydroxycrotonamide;
N-(*trans*-4-tert-butylcyclohexyl)-2-cyano-3-hydroxycrotonamide;
N-(*cis*-4-tert-butyl cyclohexyl)-2-cyano-3-hydroxycrotonamide;
N-(2-Fluoroethyl)-2-cyano-3-hydroxycrotonamide;
N,N-Diethyl-2-cyano-3-hydroxycrotonamide;
N-Ethyl-2-cyano-3-hydroxycrotonamide;
N-(2,2,2-Trifluoroethyl)-2-cyano-3-hydroxycrotonamide;
N-[2(4-Nitrophenyl)ethyl]-2-cyano-3-hydroxycrotonate;
N-Benzyl-2-cyano-3-hydroxycrotonamide;
N-Allyl-2-cyano-3-hydroxycrotonamide;
N-(2-Methoxyethyl)-2-cyano-3-hydroxycrotonamide;
N-(3-Methoxypropyl)-2-cyano-3-hydroxycrotonamide;
N-Acetonitrile-2-cyano-3-hydroxycrotonamide;
N-Propargyl-2-cyano-3-hydroxycrotonamide;
N-(2-Hydroxyethyl)-2-cyano-3-hydroxycrotonamide;
N-(4-Hydroxybutyl)-2-cyano-3-hydroxycrotonamide;
4-Trifluoromethylphenyl-2-cyano-3-hydroxycrotonimide;
3-Phenyl-1-butyl-2-cyano-3-hydroxycrotonate;
N-(Acetic acid)-2-cyano-3-hydroxycrotonamide;
N-(2-Norbornyl)-2-cyano-3-hydroxycrotoamide;
N-(3-Propionic acid)-2-cyano-3-hydroxy-crotonamide;
N-[2-(4-Chlorophenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-(2-Piperidin-1-ylethyl)-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Chlorophenyl)ethyl]-2-cyano-3-hydroxycrotonate;
N-Cyclobutylmethyl-2-cyano-3-hydroxy crotonamide;
N-(Ethylglycinate)-2-cyano-3-hydroxycrotonamide;
Cinnamyl 2-cyano-3-hydroxycrotonate;

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N-(Epi-4-Carboxycyclohexylmethyl)-2-Cyano-3-hydroxycrotonamide;
N-(2-Methylcyclohexyl)-2-cyano-3-hydroxy crotonamide;
N-(2-Hydroxy-2-phenylethyl)-2-cyano-3-hydroxycrotonamide;
N-[2-(3-Trifluoromethylphenyl)ethyl]-2-cyano-3-hydroxycrotonate;
N-(Furfuryl)-2-cyano-3-hydroxy-crotonamide;
N-[2-(4-Methoxyphenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Methylphenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-((-)-cis-Myrtanyl)-2-cyano-3-hydroxycrotonamide;
N-[2-(4-Ethylphenyl)ethy]-2-cyano-3-hydroxycrotonamide;
2-Cyano-3-hydroxy-crotonic acid aziridinyl amide;
N-[2-(4-Hydroxyphenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
2-Phenylethyl-2-cyano-3-hydroxycrotonamide;
2-Cyano-3-hydroxycrotonic 4-chlorocinnamimide;
2-Cyano-3-hydroxycrotonic cinnamimide;
(4(S)-Benzyl-2-oxazolidinone)-2-cyano-3-hydroxycrotonimide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2',4'-dichlorophenyl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-phenylcrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4'-methoxyphenyl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4'-t-butylphenyl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(*trans*-phenylcyclopropyl)-acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-biphenyl-acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(3',4',5'-tri-methoxy-phenyl)-acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-phenylcrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(4-trifluoromethylphenyl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(furan-2-yl)acrylamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-5-phenyl-penta-2,4-dienoic acid amide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-methyl-penta-2,4-dienoic acid amide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-carboxyethylcrotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-4-ethyl-oct-2-enoic acid amide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-3-(2-thienylmethyl)crotonamide;
N-(4-Trifluoromethylphenyl)-2-cyano-3-hydroxy-2,6-heptadieneamide;
(3-Furanyl)methyl 2-cyano-3-hydroxycrotonate;
2-(1-Piperidyl)ethyl 2-cyano-3-hydroxycrotonate;
3-Pyridyl 2-cyano-3-hydroxycrotonate;
4-(2-methyl-5-(p-nitrophenyl)oxazolyl)methyl 2-cyano-3-hydroxycrotonate;
7-Chloro-4-quinolyl 2-cyano-3-hydroxycrotonate;

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2-(4-Nitrophenyl)ethyl 2-cyano-3-hydroxycrotonate;
2-(4-Nitrophenyl)ethyl 4,4,4-trifluoro-2-cyano-3-hydroxycrotonate;
N-Benzyl-2-cyano-3-hydroxycrotonyl hydroxamide;
N-Benzyl-2-cyano-3-hydroxycrotonyl hydroxamide;
N-(7-Trifluoromethyl-1,2,3,4-tetrahydroquinolinyl)-2-cyano-3-hydroxycrotonamide;
N-Cycloleucyl-2-cyano-3-hydroxycrotonamide;
N-(L-Tyrosinyl methyl ester)-2-cyano-3-hydroxycrotonamide;
N-(1-Homopiperidinyl)-2-cyano-3-hydroxycrotonylhydrazide;
N-[2-(2-Carboxy)norbornyl]-2-cyano-3-hydroxycrotonamide;
N-(2-Thienylmethyl)-2-cyano-3-hydroxycrotonamide;
N-(2,6-Dimethylmorpholinyl)-2-cyano-3-hydroxycrotonamide;
N,N-Dimethylaminoethyl-2-cyano-3-hydroxycrotonamide;
N-[2-(1-Cyclohexenyl)ethyl]-2-cyano-3-hydroxycrotonamide;
N-Benzyl-N-(2-norbornyl)-2-cyano-3-hydroxycrotonamide;
N-Convolvinyl-2-cyano-3-hydroxycrotonamide;
N-(4-Propylpiperidinyl)-2-cyano-3-hydroxycrotonamide;
N-{4-[(4-Hydroxy-3-*t*-butyl)-phenoxyethoxy]phenyl}-2-cyano-3-hydroxycrotonamide;
N-4-[2-(Phenylaminocarbonyl)propionyl]phenyl-2-cyano-3-hydroxycrotonamide;
N-(2-Methyl-1-amyl)-2-cyano-3-hydroxy-4,4,4-trifluorocrotonamide;
N-(5-Morpholinylamyl)-2-cyano-3-hydroxycrotonamide;
N-(5-Diisopropylamino-1,3,4-thiadiazole-2-yl)-2-cyano-3-hydroxycrotonamide;
N-(L-Prolyl *t*-butyl ester)-2-cyano-3-hydroxycrotonamide;
N-(L-Leucyl-*t*-butyl ester)-2-cyano-3-hydroxycrotonamide;
N-(1-Cyanocyclopentylmethyl)-2-cyano-3-hydroxycrotonamide;
N-[(1-Carboxy)cycloheptyl]-N-ethyl-2-cyano-3-hydroxycrotonamide;
N-{4-[2-(2-Methoxyethoxy)ethoxy]phenyl}-2-cyano-3-hydroxycrotonamide;
N-(Glycine trityl ester)-2-cyano-3-hydroxycrotonamide;
N-{[2-(2-Chlorophenyl)]-1-oxocyclohexan-2-yl hydrochloride}-2-cyano-3-hydroxycrotonamide;
N-(5-*exo*-Norbornen-2-yl)-N-methyl-2-cyano-3-hydroxycrotonamide;
N-(β-Alanyl *t*-butyl ester)-2-cyano-3-hydroxycrotonamide;
N-Pyrrolidinyl-2-cyano-3-hydroxy-4,4,4-trifluorocrotonic acid hydrazide;
N-Morpholinyl-2-cyano-3-hydroxy-4,4,4-trifluorocrotonic acid hydrazide;
N-(3-Methylbutyl)-4,4,4-trifluoro-2-cyano-3-hydroxycrotonamide;
1-(3-Phenyl-2-cyano-3-hydroxyacryloylamido)-4-(4-toluenesulfonylamino)benzene;
N-Butyl-3-phenyl-2-cyano-3-hydroxyacrylamide;
3-Hydroxypropyl 1-(3-phenyl-2-cyano-3-hydroxyacryloyl) ketone;

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2-Methylypropyl 1-(4,4,4-trifluoro-2-cyano-3-hydroxycrotonyl) keton ;
2-Methoxyethyl 3-(4-nitrophenyl)-2-cyano-3-hydroxyacrylate;
1,1,2,2,3,3,3-Heptafluoropropyl 1-(4,4,4-trifluoro-2-cyano-3-hydroxycrotonyl) ketone;
3-Furanylmethyl 1-(4,4,4-trifluoro-2-cyano-3-hydroxycrotonyl) ketone;
N-4-(3-Nitrophenyl)thiazol-2-yl 3-(2-methoxyphenyl)-3-hydroxy-2-cyanoacrylamide;
N-(4-Trifluoromethylphenyl)-5-(2-methoxyethyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2-fluorophenyl)isoxazole-4-carboxamide;
N-(4-Fluorophenyl)-5-(4-fluorophenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(carbomethoxymethyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2-carbomethoxyethyl)isoxazole-4-carboxamide;
N-(2-Pyridyl)-5-(2-benzylphenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(3-carboethoxypropyl)isoxazole-4-carboxamide;
N-(4-*t*-Butylphenyl)-5-(methoxymethyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2-furanyl)isoxazole-4-carboxamide;
N-(2-Bromophenyl)-5-(4-hexadecyloxyphenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2,4-bis(1,1,2-trifluoro-2-chloroethoxy)phenyl) isoxazole-4-carboxamide;
N-(2-Bromophenyl)-5-(5,6,7,8-tetrahydro-2-naphthyl)isoxazole-4-carboxamide;
N-(2,5-Dimethoxyphenyl)-5-(2-thienyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(3-N,N dimethylsulfonamidophenyl)isoxazole-4-carboxamide;
N-(4-Fluorophenyl)-5-(*E* -2-phenylethylenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2-methylsulfonylphenyl)isoxazole-4-carboxamide;
N-Morpholino-5-(4-phenoxyphenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-((2-phenoxyethoxy)phenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(4-*t*-butylphenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(3-nitro-4-(2-(4-(2-(2,4,4,trimethylpentyl) phenoxy) ethoxy)phenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2-carbomethoxyphenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(2-methoxyethyl)isoxazole-4-carboxamide;
N-(2-(5-(4-t-Butylphenyl)thienyl))-5-(3-butenyl)isoxazole-4-carboxamide;
N-(4-(4-Trifluoromethylphenyl)phenyl)-5-(4-cyanophenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(6-undecyl)isoxazole-4-carboxamide
N-(4-Trifluoromethylphenyl)-5-(3,5-bis(trifluoromethyl)phenyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(1-adamantyl)isoxazole-4-carboxamide;
N-(4-Trifluoromethylphenyl)-5-(*E* -3-pentenyl)isoxazole-4-carboxamide;
4-Trifluoromethylphenyl 5-((phenylsulfonyl)methyl)isoxazole-4-carboxylate;

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